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| (54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST | | |
| (57) Abstract A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9 α ,11 α -substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone. | | |

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METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION
THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-
STEROIDAL ALDOSTERONE ANTAGONIST

5

Field of the Invention

Therapeutic methods are described for treatment of
cardiofibrosis and cardiac hypertrophy. Of particular
10 interest are therapies using an epoxy-containing steroidal
aldosterone receptor antagonist compound such as
epoxymexrenone in combination with an angiotensin II
receptor antagonist compound.

15

Background of the Invention

Myocardial (or cardiac) failure, whether a
consequence of a previous myocardial infarction, heart
disease associated with hypertension, or primary
20 cardiomyopathy, is a major health problem of worldwide
proportions. The incidence of symptomatic heart failure has
risen steadily over the past several decades.

In clinical terms, decompensated cardiac failure
25 consists of a constellation of signs and symptoms that
arises from congested organs and hypoperfused tissues to
form the congestive heart failure (CHF) syndrome.
Congestion is caused largely by increased venous pressure
and by inadequate sodium (Na⁺) excretion, relative to dietary
30 Na⁺ intake, and is importantly related to circulating levels
of aldosterone (ALDO). An abnormal retention of Na⁺ occurs
via tubular epithelial cells throughout the nephron,
including the later portion of the distal tubule and
cortical collecting ducts, where ALDO receptor sites are
35 present.

ALDO is the body's most potent mineralocorticoid
hormone. As connoted by the term mineralocorticoid, this

steroid hormone has mineral-regulating activity. It promotes Na^+ reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive tissues. ALDO regulates Na^+ and water resorption at the expense of potassium (K^+) and magnesium (Mg^{2+}) excretion.

ALDO can also provoke responses in nonepithelial cells. Elicited by a chronic elevation in plasma ALDO level that is inappropriate relative to dietary Na^+ intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as non-renin-dependent factors (such as K^+ , ACTH) that promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine its plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

The renin-angiotensin-aldosterone system (RAAS) is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension. Activation of the renin-angiotensin-aldosterone system begins with renin secretion from the juxtaglomerular cells in the kidney and culminates in the formation of angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic

effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II binding at its receptors is a viable approach to inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such peptidic compounds are of limited use due to their lack of oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, early descriptions of such non-peptidic compounds include the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid which has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and *in vivo* tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247(1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and *in vivo* tests [A. T. Chiu et al, European J. Pharmacol., 157, 31-21 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant

decrease in mean arterial blood pressure in conscious hypertensive rats. Other families of non-peptidic angiotensin II antagonists have been characterized by molecules having a biphenylmethyl moiety attached to a heterocyclic moiety. For example, EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole. U.S. Patent No. 4,880,804 to Carini et al describes a family of biphenylmethylbenzimidazole compounds as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

Many aldosterone receptor blocking drugs are known. For example, spironolactone is a drug which acts at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosterone-related diseases such as liver cirrhosis and congestive heart failure [F.J. Saunders et al, Aldactone: Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day] were administered to a spironolactone-intolerant patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug, 1986)]. It has been recognized that development of

myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to excessive collagen deposition [D. Klug et al, Am. J. Cardiol., 71 (3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G. Brilla et al, J. Mol. Cell. Cardiol., 25(5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)].

Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

Moreover, although ACE inhibitors effectively block the formation of angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, J. Endocrinol., 91, 457-465 (1981)]. A similar effect has been observed for patients with myocardial infarction receiving zofenopril [C. Borghi et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. This phenomenon has been termed "aldosterone escape".

Another series of steroidal-type aldosterone receptor antagonists is exemplified by epoxy-containing spironolactone derivatives. For example, U.S. Patent No. 4,559,332 issued to Grob et al describes 9 α ,11 α -epoxy-
5 containing spironolactone derivatives as aldosterone antagonists useful as diuretics. These 9 α ,11 α -epoxy steroids have been evaluated for endocrine effects in comparison to spironolactone [M. de Gasparo et al, J. Pharm. Exp. Ther., 240(2), 650-656 (1987)].

10

Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and that
15 aldosterone levels increase as CHF progresses from activation of the Renin-Angiotensin-Aldosterone System (RAAS). Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and
20 transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and
25 spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. Cardiol., 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of captopril and spironolactone was administered and found effective to control refractory CHF without
30 serious incidents of hyperkalemia [U. Dahlstrom et al, Am. J. Cardiol., 71, 29A-33A (21 Jan 1993)]. Spironolactone coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure [A.A. van Vliet et al, Am. J.
35 Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to

determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)].

- 5 Combinations of an angiotensin II receptor
antagonist and aldosterone receptor antagonist, are known.
For example, PCT Application No. US91/09362 published 25
June 1992 describes treatment of hypertension using a
combination of an imidazole-containing angiotensin II
10 antagonist compound and a diuretic such as spironolactone.

Summary of the Invention

A therapeutic method for treating or preventing the progression of cardiofibrosis or cardiac hypertrophy is provided by a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist.

The phrase "angiotensin II receptor antagonist" is intended to embrace one or more compounds or agents having the ability to interact with a receptor site located on various human body tissues, which site is a receptor having a relatively high affinity for angiotensin II and which receptor site is associated with mediating one or more biological functions or events such as vasoconstriction or vasorelaxation, kidney-mediated sodium and fluid retention, sympathetic nervous system activity, and in modulating secretion of various substances such as aldosterone, vasopressin and renin, to lower blood pressure in a subject susceptible to or afflicted with elevated blood pressure. Interactions of such angiotensin II receptor antagonist with this receptor site may be characterized as being either "competitive" (i.e., "surmountable") or as being "insurmountable". These terms, "competitive" and "insurmountable", characterize the relative rates, faster for the former term and slower for the latter term, at which the antagonist compound dissociates from binding with the receptor site.

The phrase "epoxy-steroidal aldosterone receptor antagonist" is intended to embrace one or more agents or compounds characterized by a steroid-type nucleus and having an epoxy moiety attached to the nucleus and which agent or compound binds to the aldosterone receptor, as a competitive inhibitor of the action of aldosterone itself at the receptor site, so as to modulate the receptor-mediated activity of aldosterone.

The phrase "combination therapy", in defining use of an angiotensin II antagonist and an epoxy-steroidal aldosterone receptor antagonist, is intended to embrace administration of each antagonist in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended to embrace co-administration of the antagonist agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each antagonist agent.

The phrase "therapeutically-effective" is intended to qualify the amount of each antagonist agent for use in the combination therapy which will improve cardiac sufficiency by reducing or preventing the progression of myocardial fibrosis or cardiac hypertrophy.

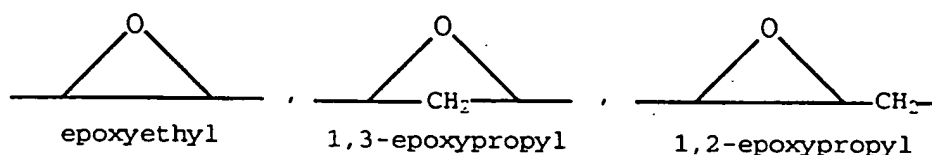
Another combination therapy of interest would consist essentially of three active agents, namely, an AII antagonist, an aldosterone receptor antagonist agent and a diuretic.

For a combination of AII antagonist agent and an ALDO antagonist agent, the agents would be used in combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of the AII antagonist agent to the aldosterone receptor antagonist agent. A preferred range of these two agents (AII antagonist-to-ALDO antagonist) would be from about one-to-one to about fifteen-to-one, while a more preferred range would be from about one-to-one to about five-to-one, depending ultimately on the selection of the AII antagonist and ALDO antagonist. The diuretic agent may be present in a ratio range of 0.1-to-one to about ten to one (AII antagonist to diuretic).

Detailed Description of the Invention

Epoxy-steroidal aldosterone receptor antagonist compounds suitable for use in the combination therapy consist of these compounds having a steroidal nucleus substituted with an epoxy-type moiety. The term "epoxy-type" moiety is intended to embrace any moiety characterized in having an oxygen atom as a bridge between two carbon atoms, examples of which include the following moieties:

10



The term "steroidal", as used in the phrase "epoxy-steroidal", denotes a nucleus provided by a cyclopentenophenanthrene moiety, having the conventional "A", "B", "C" and "D" rings. The epoxy-type moiety may be attached to the cyclopentenophenanthrene nucleus at any attachable or substitutable positions, that is, fused to one of the rings of the steroidal nucleus or the moiety may be substituted on a ring member of the ring system. The phrase "epoxy-steroidal" is intended to embrace a steroidal nucleus having one or a plurality of epoxy-type moieties attached thereto.

Epoxy-steroidal aldosterone receptor antagonists suitable for use in combination therapy include a family of compounds having an epoxy moiety fused to the "C" ring of the steroidal nucleus. Especially preferred are 20-spiroxane compounds characterized by the presence of a 9 α ,11 α -substituted epoxy moiety. Table I, below, describes a series of 9 α ,11 α -epoxy-steroidal compounds which may be used in the combination therapy. These epoxy steroids may be prepared by procedures described in U.S. Patent No. 4,559,332 to Grob et al issued 17 December 1985.

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name |
|------------|-----------|---|
| 1 | | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ -lactone, methyl ester, (7 α ,11 α .,17 α) - |
| 2 | | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 α ,11 α ,17 α) - |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name |
|------------|-----------|--|
| 3 | | 3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -lactone, (6 β ,7 β ,11 β ,17 β)- |
| 4 | | Pregn-4-ene-7,21-dicarboxylic acid,9,11-epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt, (7a,11a,17a)- |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name |
|------------|-----------|--|
| 5 | | Pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-17-hydroxy-3-oxo-,7-methyl ester, monopotassium salt, (7a,11a,17a)- |
| 6 | | 3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g-lactone(6a,7a,11.a)- |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name |
|------------|-----------|--|
| 7 | | 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6a,7a,11a,17a)- |
| 8 | | 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6a,7a,11a,17a)- |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name |
|------------|-----------|--|
| 9 | | 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, g lactone, (6a,7a,11a.,17a)- |
| 10 | | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, ethyl ester, (7a,11a,17a)- |

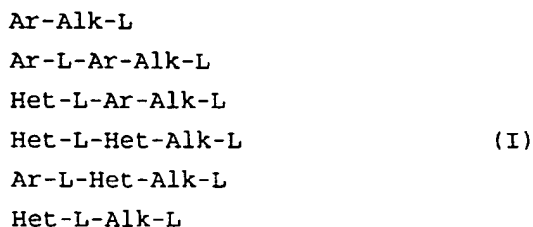
TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name |
|------------|-----------|--|
| 11 | | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, 1-methylethyl ester, (7a,11a,17a)- |

Angiotensin II receptor antagonist compounds suitable for use in the combination therapy are described in Table II, below. Preferred compounds for use in the combination therapy may be generally characterized structurally as having two portions. A first portion constitutes a mono-aryl-alkyl moiety, or a bi-aryl-alkyl moiety, or a mono-heteroaryl-alkyl moiety, or a bi-heteroaryl-alkyl moiety. A second portion constitutes a heterocyclic moiety or an open chain hetero-atom-containing moiety.

Typically, the first-portion mono/bi-aryl/heteroaryl-alkyl moiety is attached to the second portion heterocyclic/open-chain moiety through the alkyl group of the mono/bi-aryl/heteroaryl-alkyl moiety to any substitutable position on the heterocyclic/open-chain moiety second portion. Suitable first-portion mono/bi-aryl/heteroaryl-alkyl moieties are defined by any of the various moieties listed under Formula I:

20



25

wherein the abbreviated notation used in the moieties of Formula I is defined as follows:

30

"Ar" means a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being typically fully unsaturated but which also may be partially or fully saturated. "Phenyl" radical most typically exemplifies "Ar".

35

"Het" means a monocyclic or bicyclic fused ring

system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as
5 ring members.

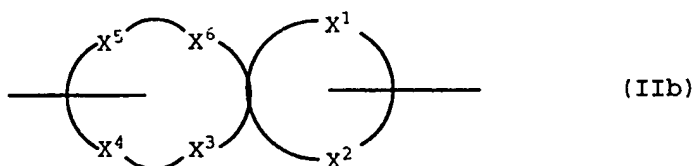
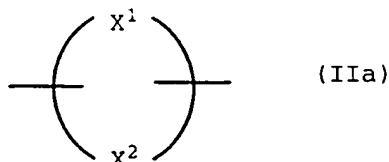
"Alk" means an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms. Typically, "Alk" means "methylene", i.e., -CH₂-.

10

"L" designates a single bond or a bivalent linker moiety selected from carbon, oxygen and sulfur. When "L" is carbon, such carbon has two hydrido atoms attached thereto.

15

Suitable second-portion heterocyclic moieties of the angiotensin II antagonist compounds, for use in the combination therapy, are defined by any of the various moieties listed under Formula IIa or IIb:



wherein each of X^1 through X^6 is selected from $-CH=$, $-CH_2-$,
 5 $-N=$, $-NH-$, O , and S , with the proviso that at least one of
 X^1 through X^6 in each of Formula IIa and Formula IIb must be
 a hetero atom. The heterocyclic moiety of Formula IIa or
 IIb may be attached through a bond from any ring member of
 the Formula IIa or IIb heterocyclic moiety having a
 10 substitutable or a bond-forming position.

Examples of monocyclic heterocyclic moieties of
 Formula IIa include thienyl, furyl, pyranyl, pyrrolyl,
 imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl,
 15 pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl,
 furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl,
 isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-
 triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl,
 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl,
 20 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-
 dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-
 dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl,
 1,4-pyranyl, 1,2-pyranyl, 1,4-pyranyl, pyridinyl,
 25 piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-
 oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl, 1,2,6-oxazinyl,
 1,4-oxazinyl, *o*-isoxazinyl, *p*-isoxazinyl, 1,2,5-
 oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl,

1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

Examples of bicyclic heterocyclic moieties of Formula IIb include benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyll, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyll, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyll, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiolo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

The angiotensin II receptor antagonist compounds, as provided by the first-and-second-portion moieties of Formula I and II, are further characterized by an acidic moiety attached to either of said first-and-second-portion moieties. Preferably this acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

-U_nA (III)

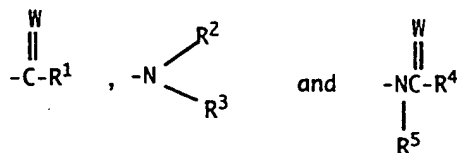
wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the -U_nA

moiety, is intended to embrace chemical groups which, when attached to any substitutable position of the Formula I-IIa/b moiety, confers acidic character to the compound of Formula I-IIa/b. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I-IIa/b to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I-IIa/b has a pK_a in a range from about one to about twelve. More typically, the Formula I-IIa/b compound would have a pK_a in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group (-COOH). Where n is zero and A is -COOH, in the $-U_nA$ moiety, such carboxyl group would be attached directly to one of the Formula I-IIa/b positions. The Formula I-IIa/b compound may have one $-U_nA$ moiety attached at one of the Formula I-IIa/b positions, or may have a plurality of such $-U_nA$ moieties attached at more than one of the Formula I-IIa/b positions. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I-IIa/b may have one or more acidic protons and, therefore, may have one or more pK_a values. It is preferred, however, that at least one of these pK_a values of the Formula I-IIa/b compound as conferred by the $-U_nA$ moiety be in a range from about two to about seven. The $-U_nA$ moiety may be attached to one of the Formula I-IIa/b positions through any portion of the $-U_nA$ moiety which results in a Formula I-IIa/b compound being relatively stable and also having a labile or acidic proton to meet the foregoing pK_a criteria. For example, where the $-U_nA$ acid moiety is tetrazole, the tetrazole is typically attached at

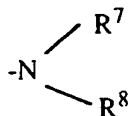
the tetrazole ring carbon atom.

For any of the moieties embraced by Formula I and Formula II, such moieties may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl, aralkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



20

wherein W is oxygen atom or sulfur atom; wherein each of R¹ through R⁵ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR⁶ and



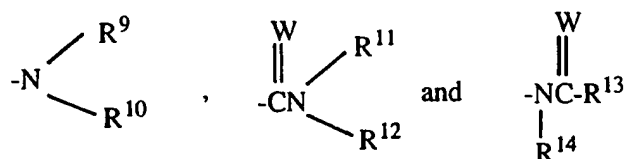
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wherein Y is selected from oxygen atom and sulfur atom and R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl,

30

arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is further independently selected from amino and amido radicals of the formula

5



wherein W is oxygen atom or sulfur atom;
 wherein each of R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ is
 10 independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl; and wherein each of R² and R³ taken together and each of R⁴ and R⁵ taken together may form a heterocyclic group having five
 15 to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially
 20 unsaturated; wherein each of R² and R³ taken together and each of R⁷ and R⁸ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more
 25 hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The combination therapy of the invention would be
 30 useful in treating myocardial fibrosis or cardiac hypertrophy, particularly left ventricular hypertrophy. The combination therapy would also be useful with adjunctive therapies. For example, the combination therapy may be used in combination with other drugs, such as a diuretic, to aid

in treatment of hypertension.

Table II, below, contains description of
angiotensin II antagonist compounds which may be used in the
5 combination therapy. Associated with each compound listed
in Table II is a published patent document describing the
chemical preparation of the angiotensin II antagonist
compound as well as the biological properties of such
compound. The content of each of these patent documents is
10 incorporated herein by reference.

TABLE II: Angiotensin II Antagonists

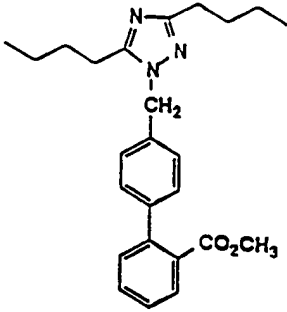
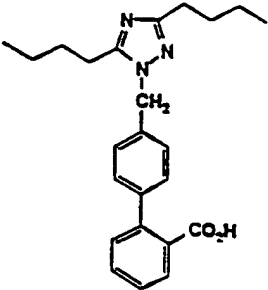
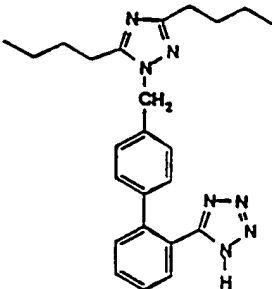
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| 3 |  | WO #91/17148 pub. 14 Nov 91 |

TABLE II: Angiotensin II Antagonists

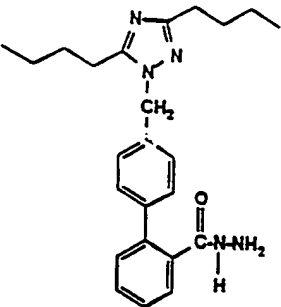
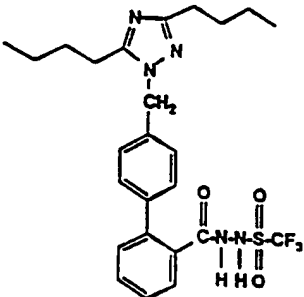
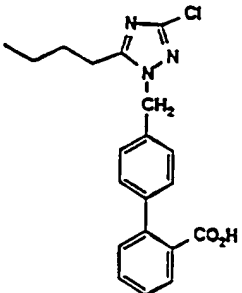
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TABLE II: Angiotensin II Antagonists

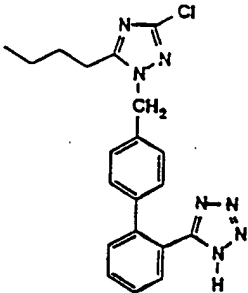
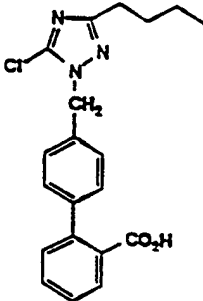
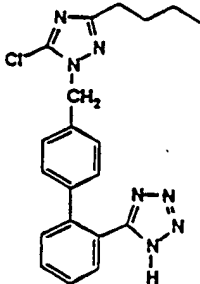
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| 9 |  | WO #91/17148 pub. 14 Nov 91 |

TABLE II: Angiotensin II Antagonists

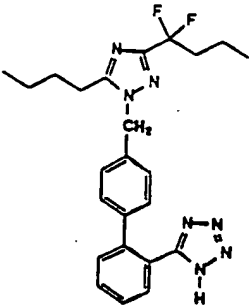
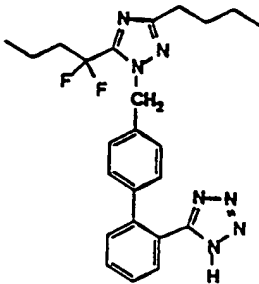
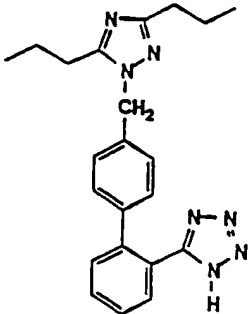
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TABLE II: Angiotensin II Antagonists

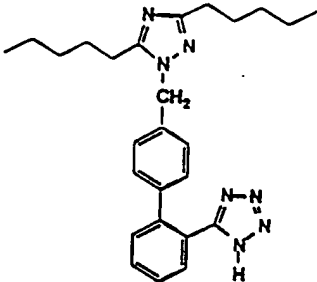
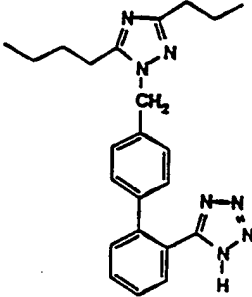
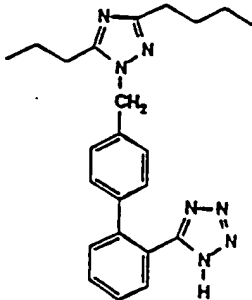
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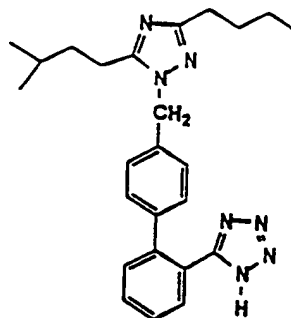
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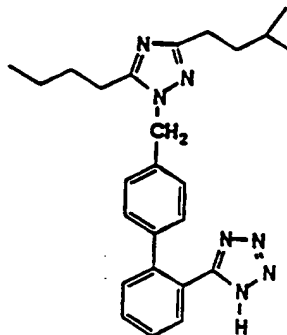
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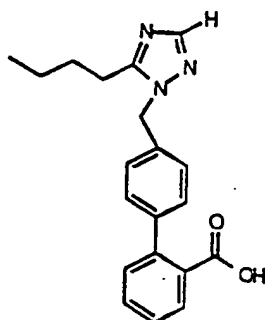
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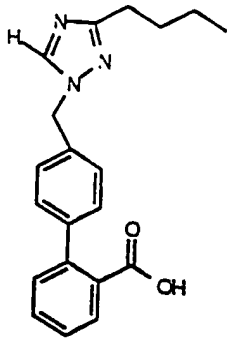
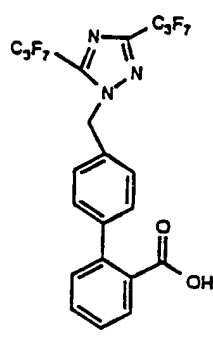
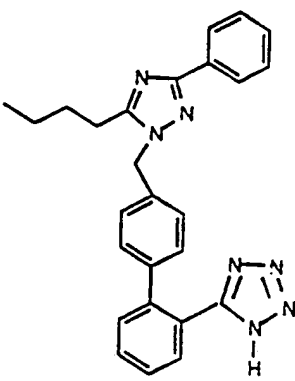
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| 19 |  | WO #91/17148 pub. 14 Nov 91 |
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TABLE II: Angiotensin II Antagonists

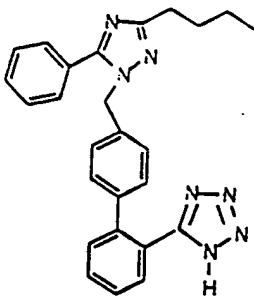
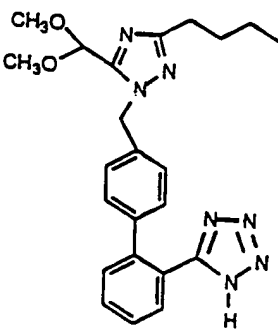
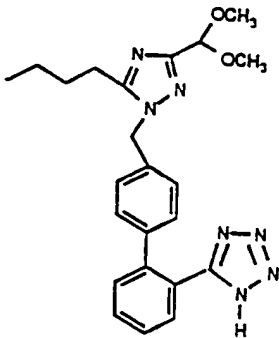
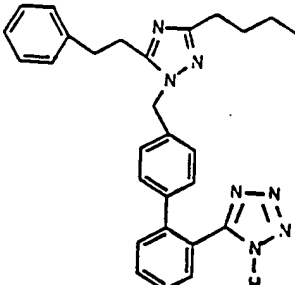
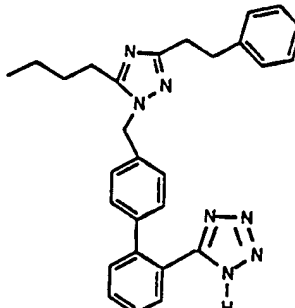
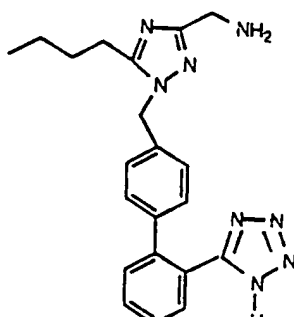
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| 24 |  | WO #91/17148 pub. 14 Nov 91 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
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| 25 |  | WO #91/17148 pub. 14 Nov 91 |
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| 27 |  | WO #91/17148 pub. 14 Nov 91 |

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TABLE II: Angiotensin II Antagonists

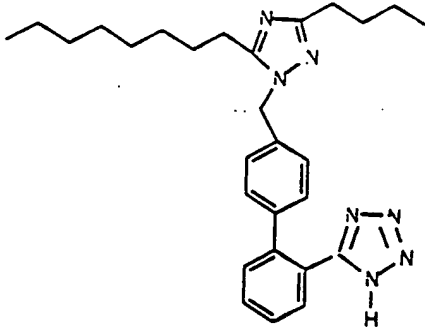
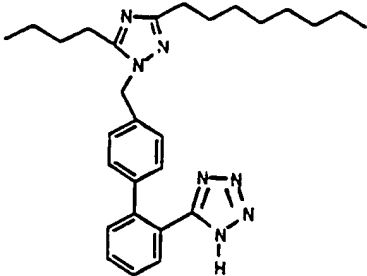
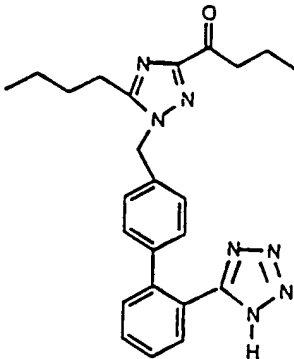
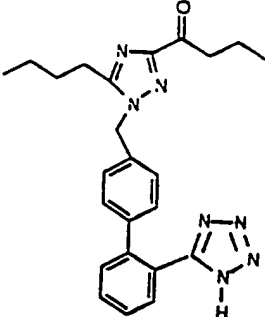
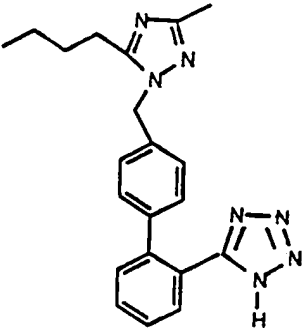
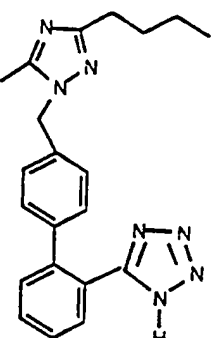
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TABLE II: Angiotensin II Antagonists

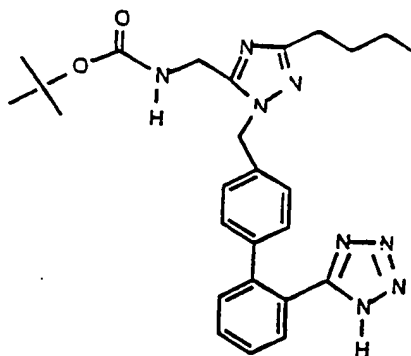
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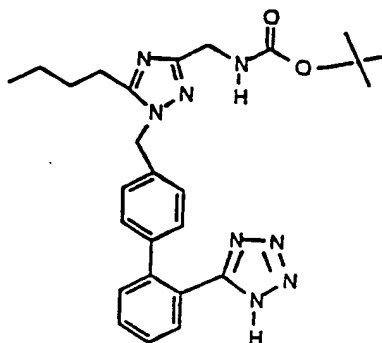
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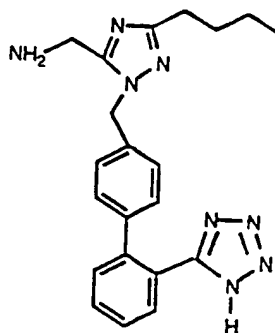
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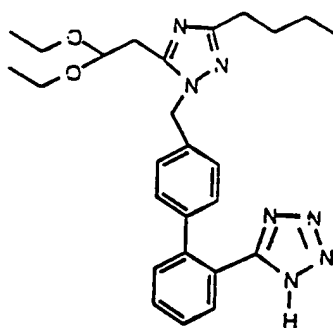
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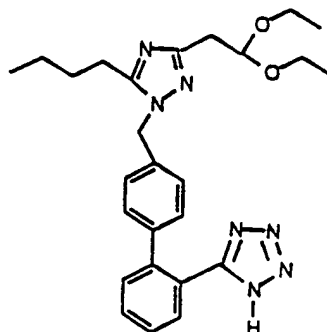
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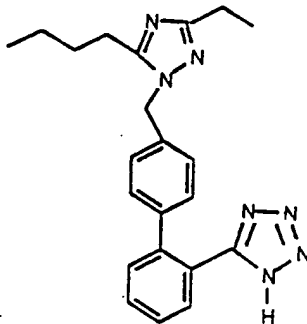
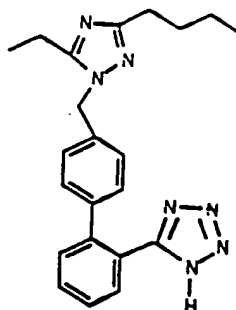
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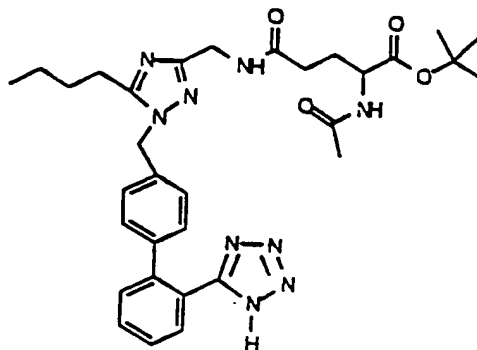
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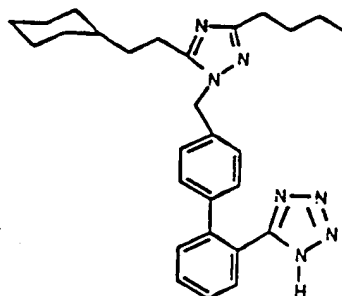
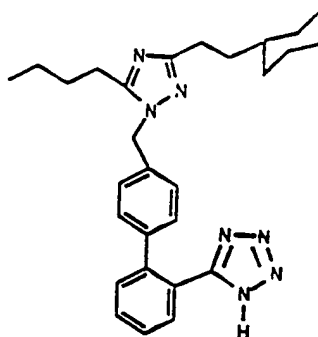
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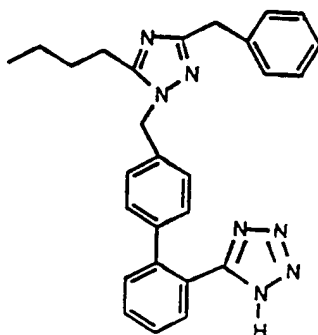
TABLE II: Angiotensin II Antagonists

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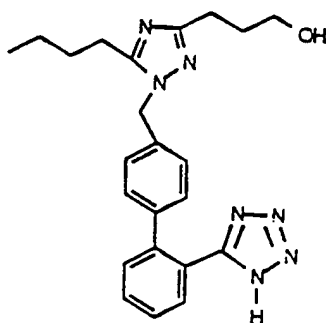
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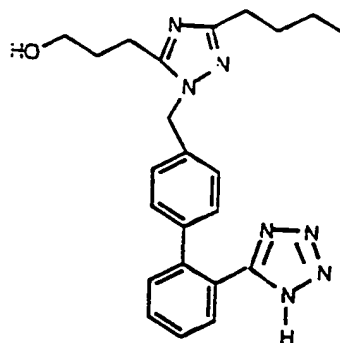
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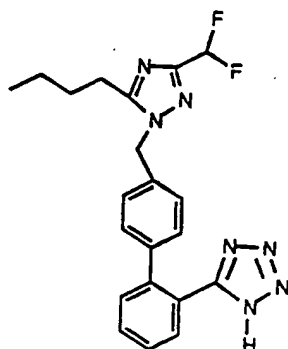
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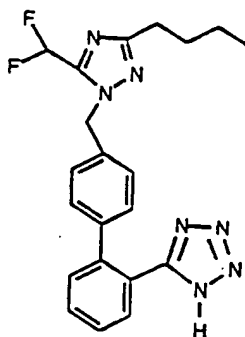
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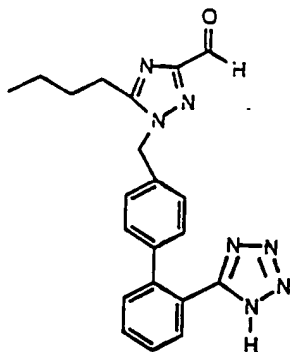
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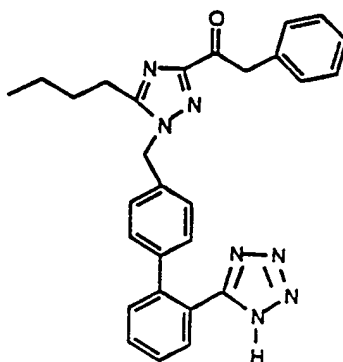
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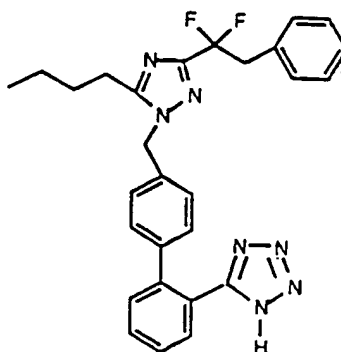
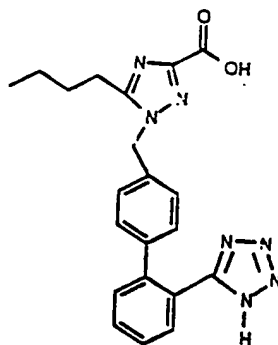
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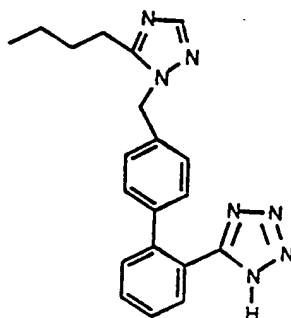
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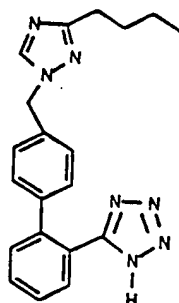
WO #91/17148
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TABLE II: Angiotensin II Antagonists

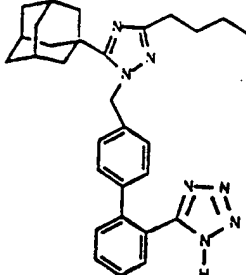
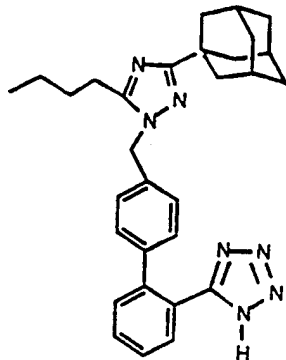
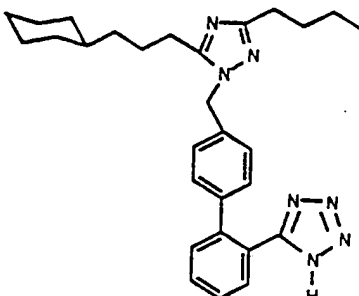
| Compound # | Structure | Source |
|------------|--|--------------------------------|
| 55 |  | WO #91/17148 pub. 14 Nov 91 |
| 56 |  | WO #91/17148 pub. 14 Nov 91 |
| 57 |  | WO #91/17148 pub. 14 Nov 91 |

TABLE II: Angiotensin II Antagonists

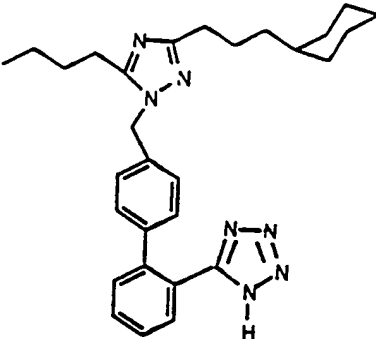
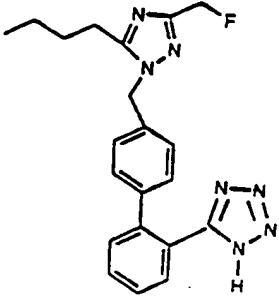
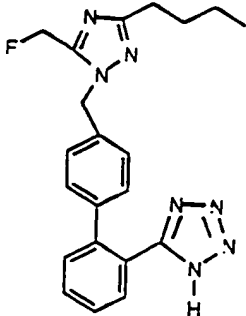
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 58 |  | WO #91/17148 pub. 14 Nov 91 |
| 59 |  | WO #91/17148 pub. 14 Nov 91 |
| 60 |  | WO #91/17148 pub. 14 Nov 91 |

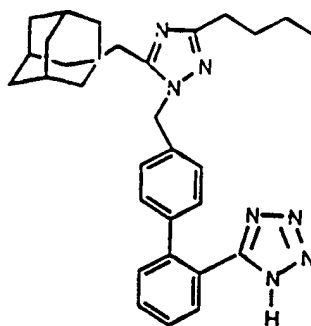
TABLE II: Angiotensin II Antagonists

Compound #

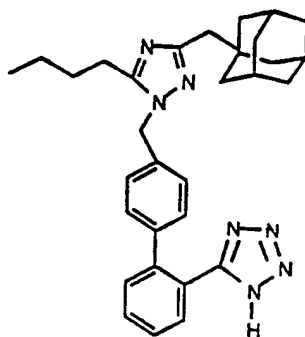
Structure

Source

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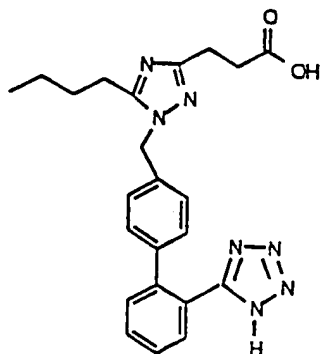
WO #91/17148
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TABLE II: Angiotensin II Antagonists

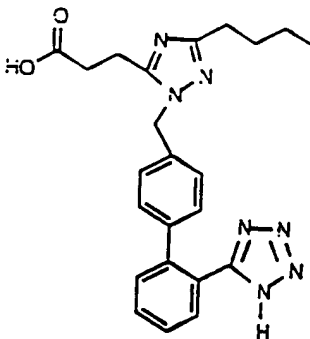
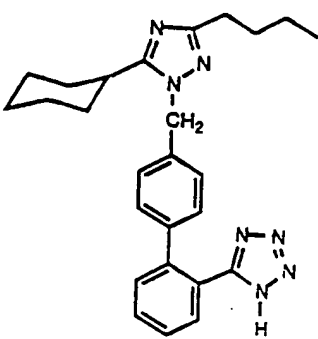
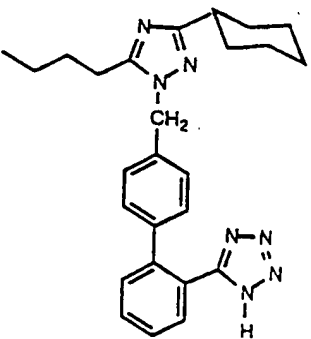
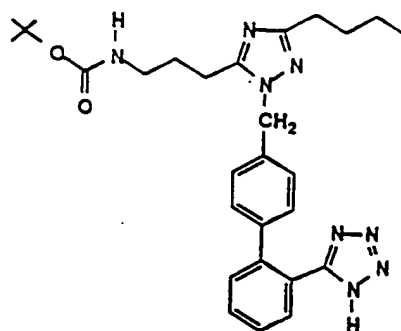
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 64 |  | WO #91/17148 pub. 14 Nov 91 |
| 65 |  | WO #91/17148 pub. 14 Nov 91 |
| 66 |  | WO #91/17148 pub. 14 Nov 91 |

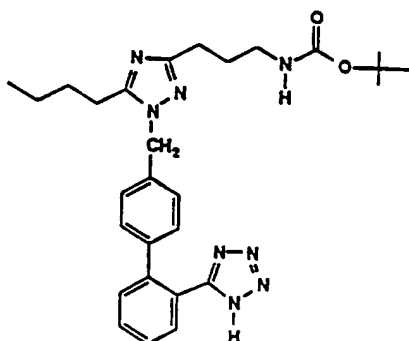
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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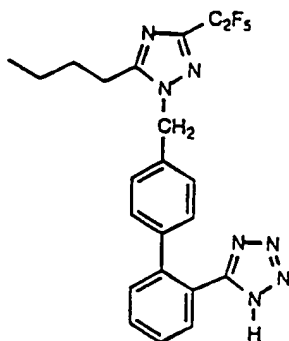
WO #91/17148
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TABLE II: Angiotensin II Antagonists

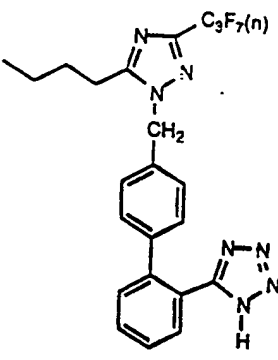
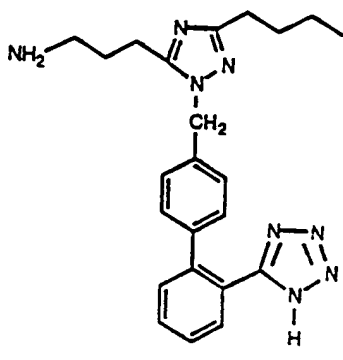
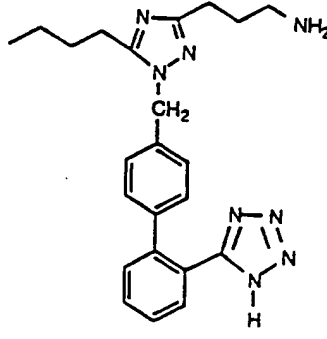
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 70 |  | WO #91/17148 pub. 14 Nov 91 |
| 71 |  | WO #91/17148 pub. 14 Nov 91 |
| 72 |  | WO #91/17148 pub. 14 Nov 91 |

TABLE II: Angiotensin II Antagonists

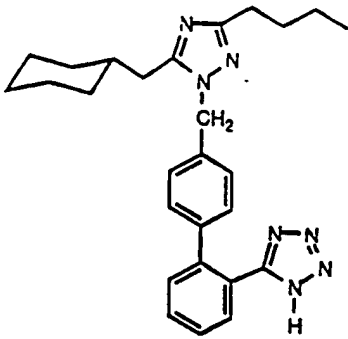
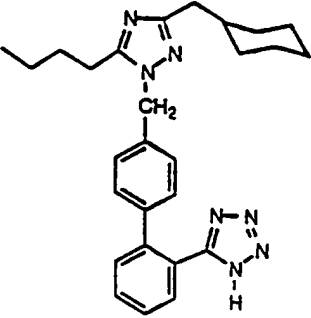
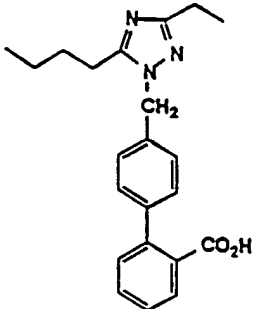
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 73 |  | WO #91/17148 pub. 14 Nov 91 |
| 74 |  | WO #91/17148 pub. 14 Nov 91 |
| 75 |  | WO #91/17148 pub. 14 Nov 91 |

TABLE II: Angiotensin II Antagonists

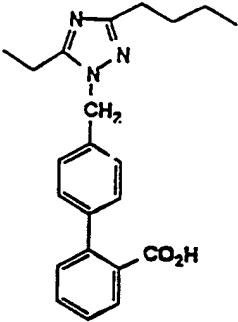
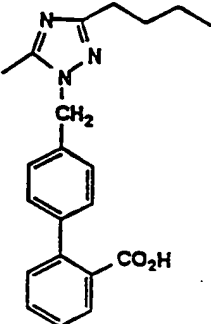
| Compound # | Structure | Source |
|------------|--|--------------------------------|
| 76 |  | WO #91/17148 pub. 14 Nov 91 |
| 77 |  | WO #91/17148 pub. 14 Nov 91 |

TABLE II: Angiotensin II Antagonists

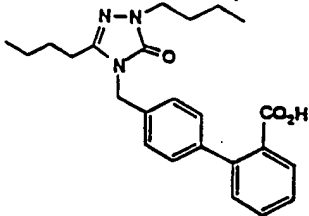
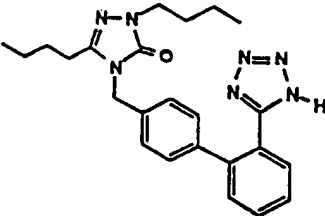
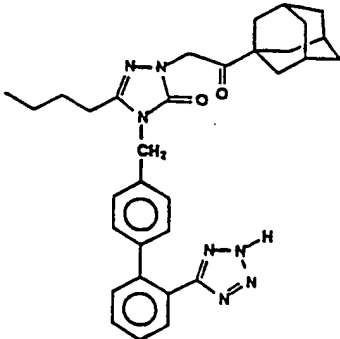
| Compound # | Structure | Source |
|------------|---|----------------------|
| 78 |  | WO #91/18888 pub. |
| 79 |  | WO #91/18888 pub. |
| 80 |  | WO #91/18888 pub. |

TABLE II: Angiotensin II Antagonists

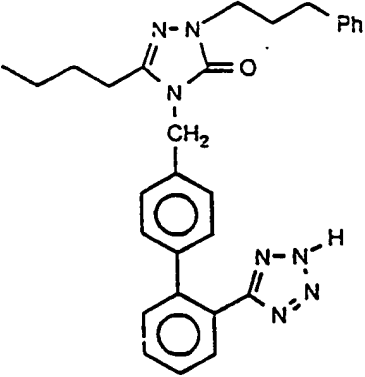
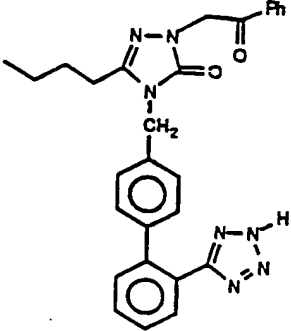
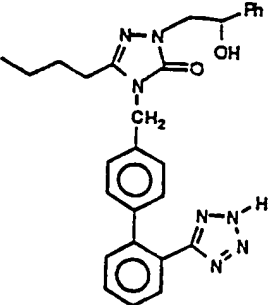
| Compound # | Structure | Source |
|------------|---|----------------------|
| 81 |  | WO #91/18888 pub. |
| 82 |  | WO #91/18888 pub. |
| 83 |  | WO #91/18888 pub. |

TABLE II: Angiotensin II Antagonists

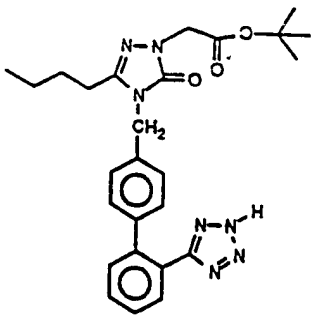
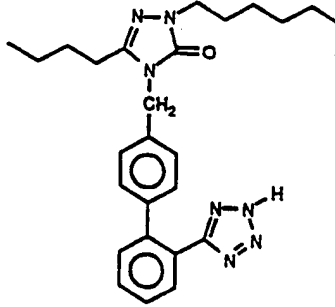
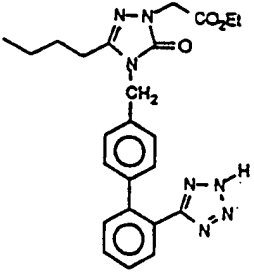
| Compound # | Structure | Source |
|------------|---|----------------------|
| 84 |  | WO #91/18888 pub. |
| 85 |  | WO #91/18888 pub. |
| 86 |  | WO #91/18888 pub. |

TABLE II: Angiotensin II Antagonists

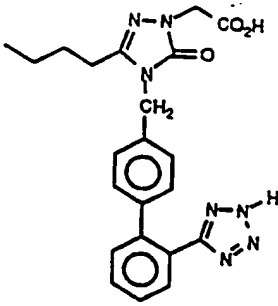
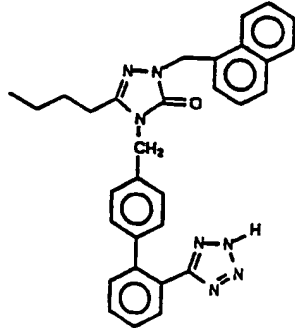
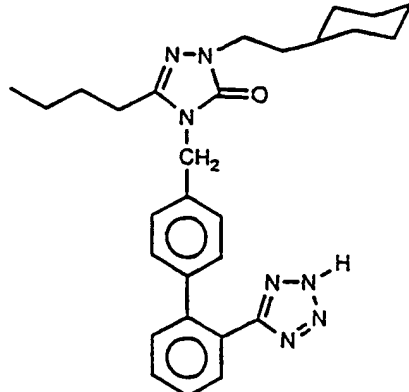
| Compound # | Structure | Source |
|------------|---|----------------------|
| 87 |  | WO #91/18888 pub. |
| 88 |  | WO #91/18888 pub. |
| 89 |  | WO #91/18888 pub. |

TABLE II: Angiotensin II Antagonists

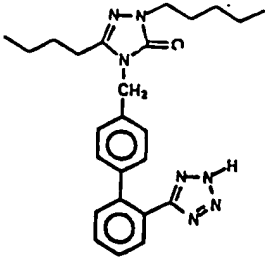
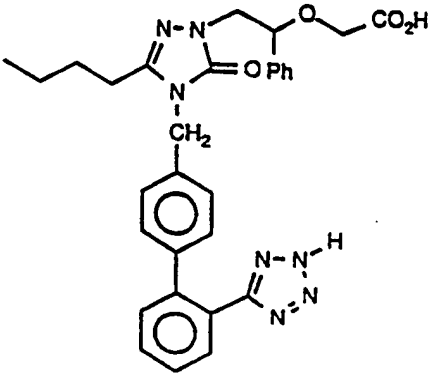
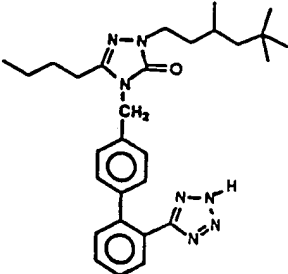
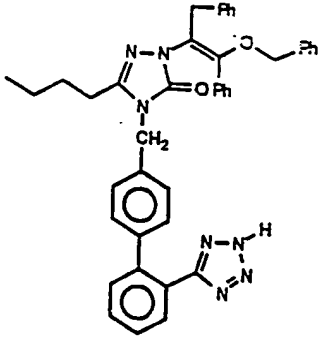
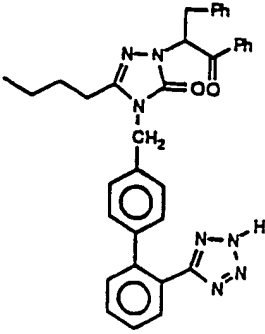
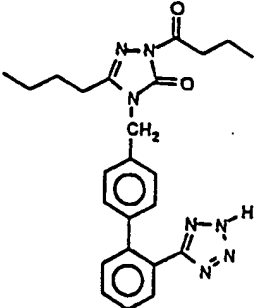
| Compound # | Structure | Source |
|------------|---|----------------------|
| 90 |  | WO #91/18888 pub. |
| 91 |  | WO #91/18888 pub. |
| 92 |  | WO #91/18888 pub. |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|---|----------------------|
| 93 |  | WO #91/18888 pub. |
| 94 |  | WO #91/18888 pub. |
| 95 |  | WO #91/18888 pub. |

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TABLE II: Angiotensin II Antagonists

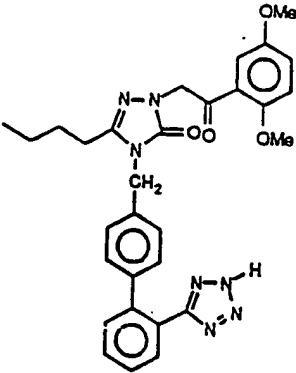
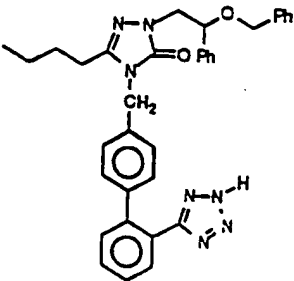
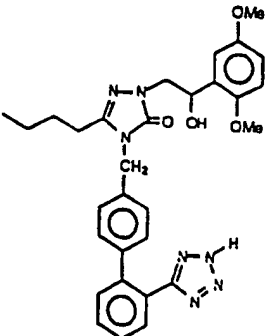
| Compound # | Structure | Source |
|------------|---|----------------------|
| 96 |  | WO #91/18888 pub. |
| 97 |  | WO #91/18888 pub. |
| 98 |  | WO #91/18888 pub. |

TABLE II: Angiotensin II Antagonists

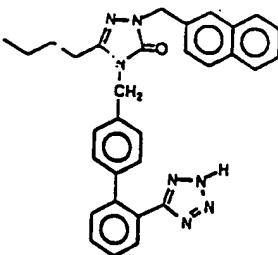
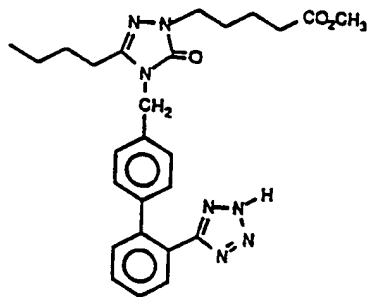
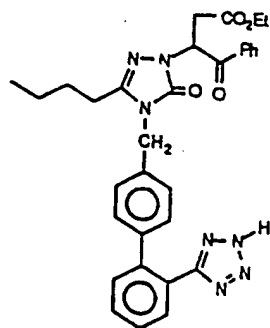
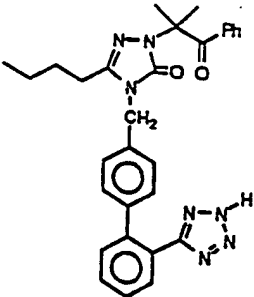
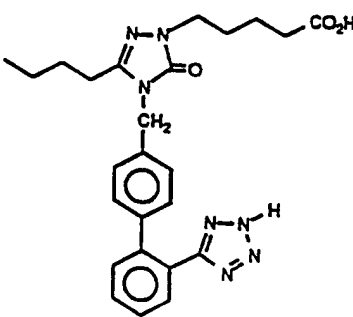
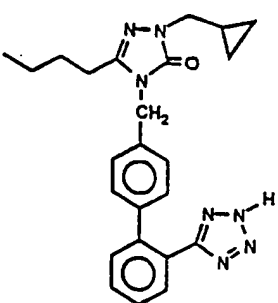
| Compound # | Structure | Source |
|------------|---|----------------------|
| 99 |  | WO #91/18888 pub. |
| 100 |  | WO #91/18888 pub. |
| 101 |  | WO #91/18888 pub. |

TABLE II: Angiotensin II Antagonists

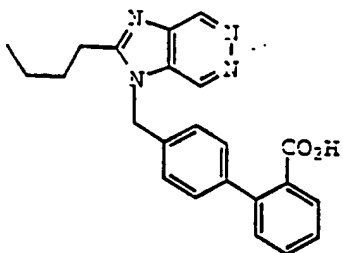
| Compound # | Structure | Source |
|------------|---|----------------------|
| 102 |  | WO #91/18888 pub. |
| 103 |  | WO #91/18888 pub. |
| 104 |  | WO #91/18888 pub. |

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TABLE II: Angiotensin II Antagonists

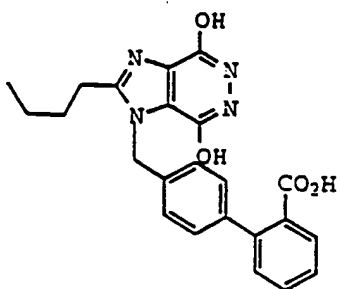
| Compound # | Structure | Source |
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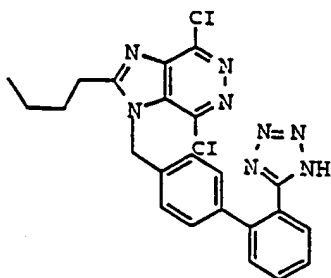
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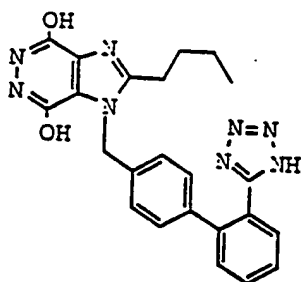


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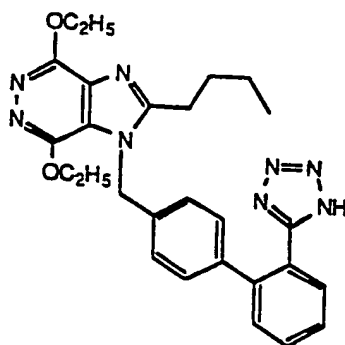
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
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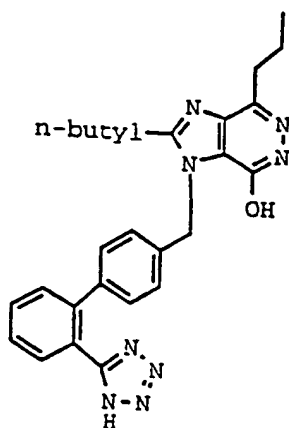
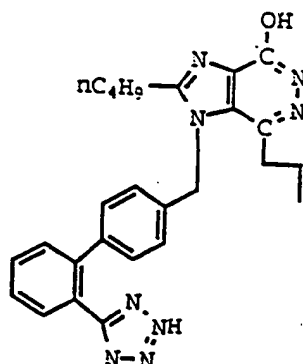
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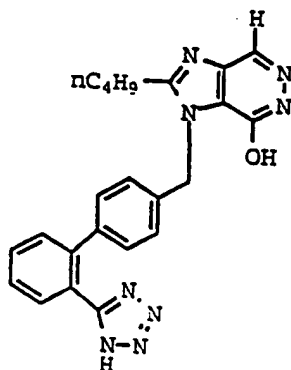
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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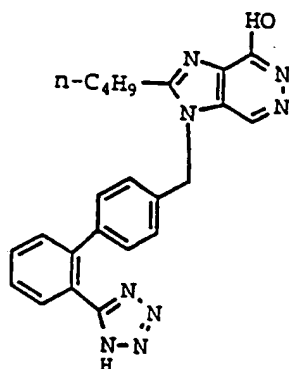
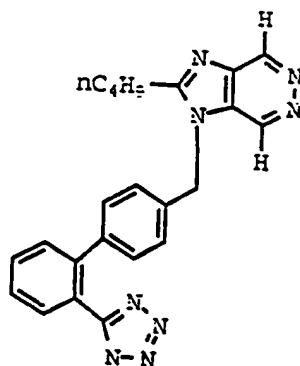
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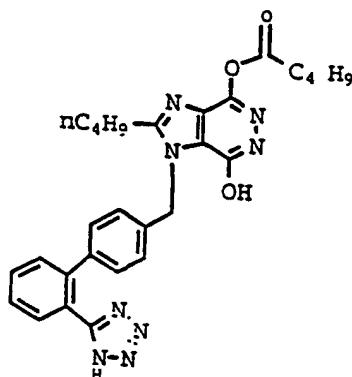
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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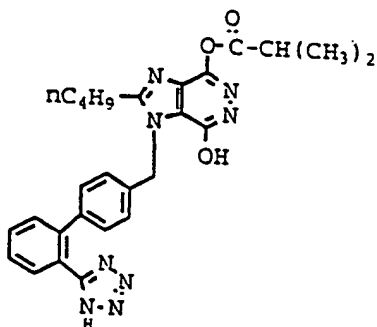
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TABLE II: Angiotensin II Antagonists

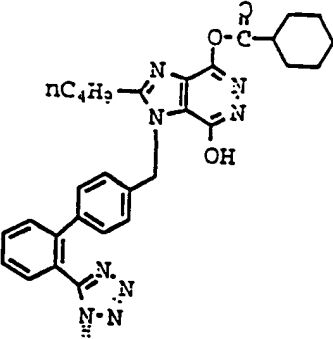
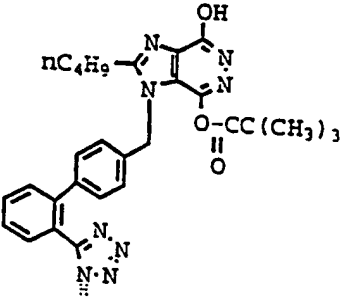
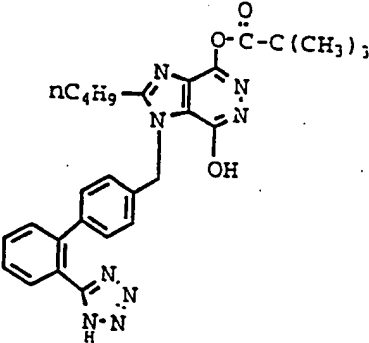
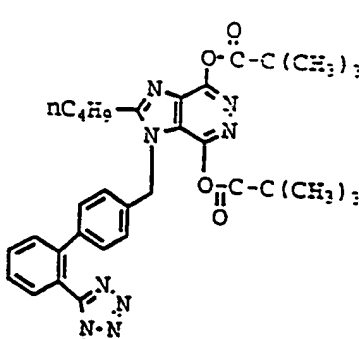
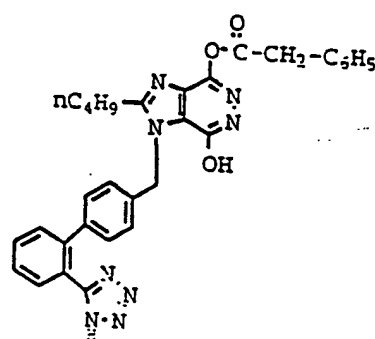
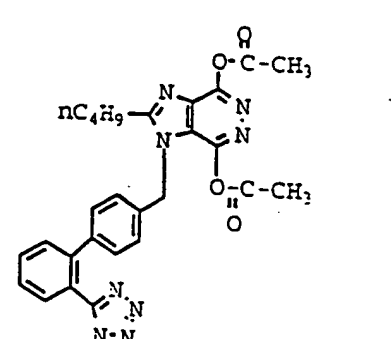
| Compound # | Structure | Source |
|------------|--|--------------------------------|
| 120 |  | WO #91/19715 pub. 26 Dec 91 |
| 121 |  | WO #91/19715 pub. 26 Dec 91 |
| 122 |  | WO #91/19715 pub. 26 Dec 91 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|--|--------------------------------|
| 123 |  | WO #91/19715 pub. 26 Dec 91 |
| 124 |  | WO #91/19715 pub. 26 Dec 91 |
| 125 |  | WO #91/19715 pub. 26 Dec 91 |

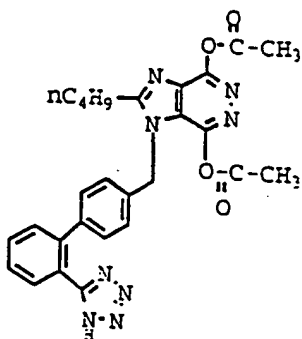
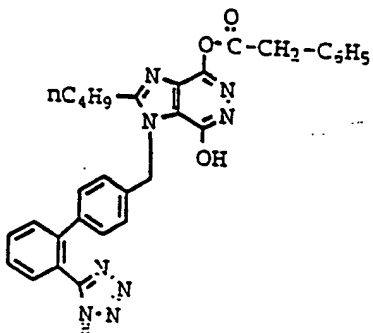
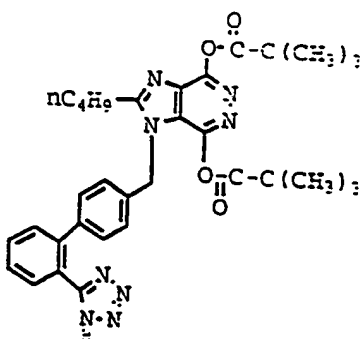


TABLE II: Angiotensin II Antagonists

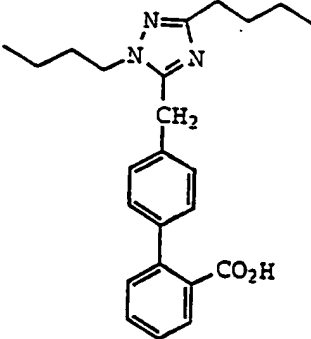
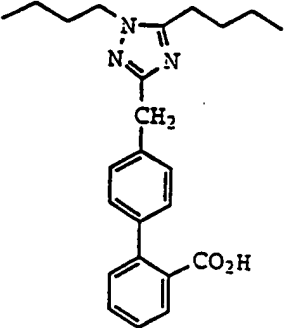
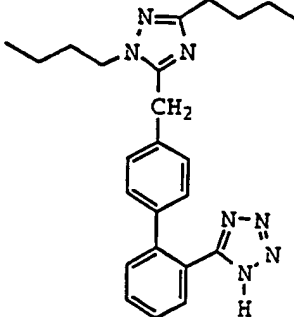
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 126 |  | WO #92/05161 pub. 2 Apr 92 |
| 127 |  | WO #92/05161 pub. 2 Apr 92 |
| 128 |  | WO #92/05161 pub. 2 Apr 92 |

TABLE II: Angiotensin II Antagonists

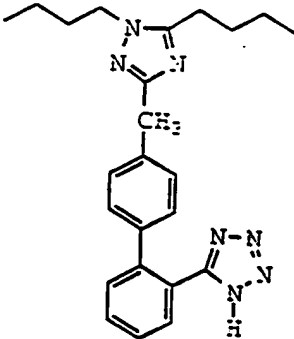
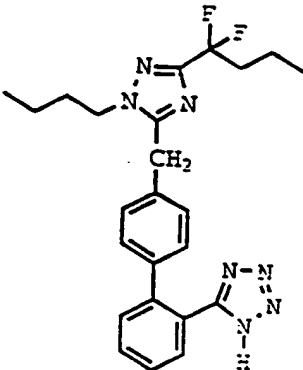
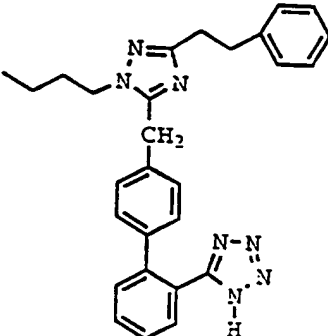
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 129 |  | WO #92/05161 pub. 2 Apr 92 |
| 130 |  | WO #92/05161 pub. 2 Apr 92 |
| 131 |  | WO #92/05161 pub. 2 Apr 92 |

TABLE II: Angiotensin II Antagonists

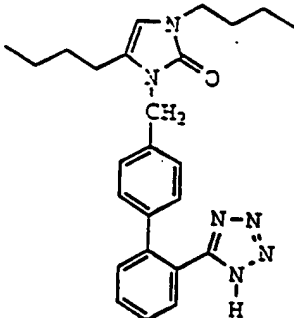
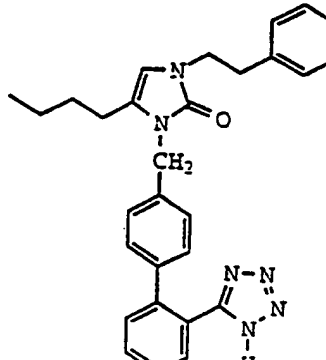
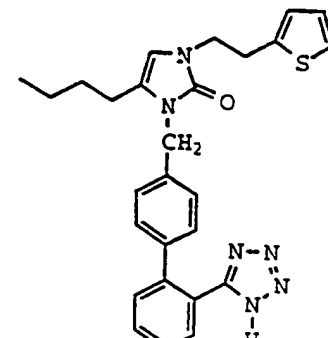
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 132 |  | WO #92/07834 pub. 14 May 92 |
| 133 |  | WO #92/07834 pub. 14 May 92 |
| 134 |  | WO #92/07834 pub. 14 May 92 |

TABLE II: Angiotensin II Antagonists

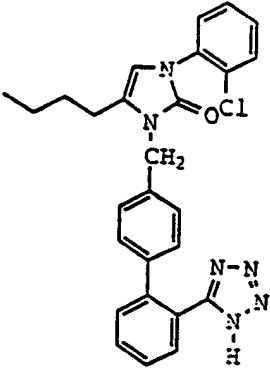
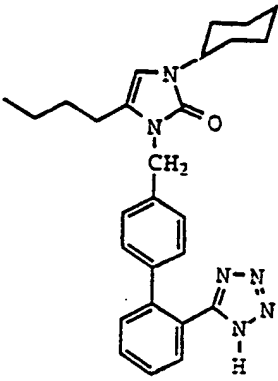
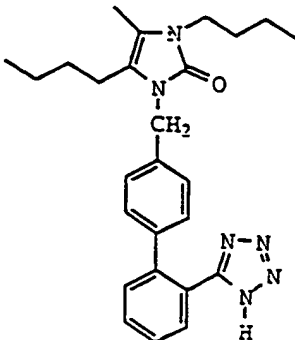
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 135 |  | WO #92/07834 pub. 14 May 92 |
| 136 |  | WO #92/07834 pub. 14 May 92 |
| 137 |  | WO #92/07834 pub. 14 May 92 |

TABLE II: Angiotensin II Antagonists

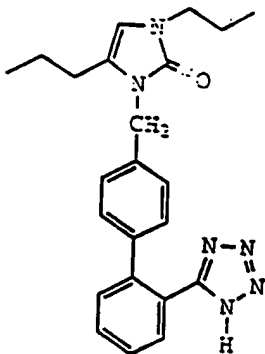
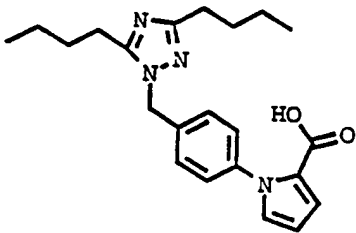
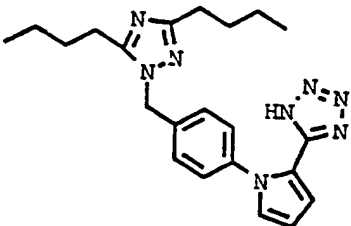
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 138 |  | WO #92/07834 pub. 14 May 92 |
| 139 |  | WO #92/11255 pub. 9 Jul 92 |
| 140 |  | WO #92/11255 pub. 9 Jul 92 |

TABLE II: Angiotensin II Antagonists

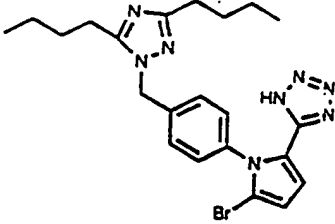
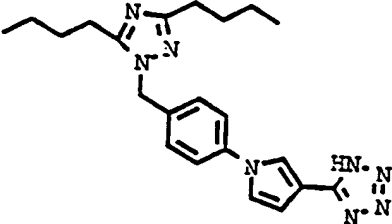
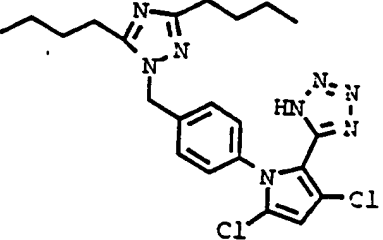
| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 141 |  | WO #92/11255 pub. 9 Jul 92 |
| 142 |  | WO #92/11255 pub. 9 Jul 92 |
| 143 |  | WO #92/11255 pub. 9 Jul 92 |

TABLE II: Angiotensin II Antagonists

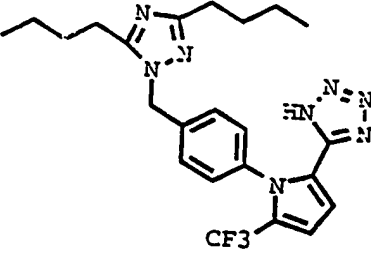
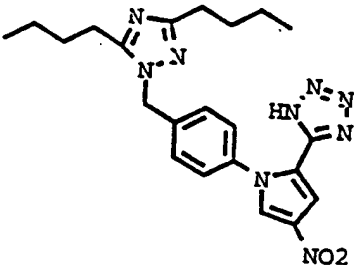
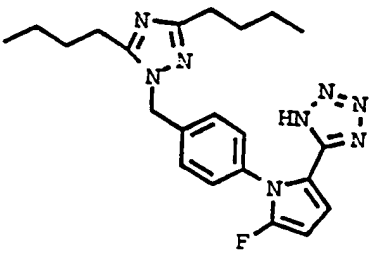
| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 144 |  <chem>CCCC1=CN=C(N1Cc2ccc(cc2)N3C=CN(C3)C4=CC=CC=C4C(F)(F)F)C</chem> | WO #92/11255 pub. 9 Jul 92 |
| 145 |  <chem>CCCC1=CN=C(N1Cc2ccc(cc2)N3C=CN(C3)C4=CC=CC=C4[N+](=O)[O-])C</chem> | WO #92/11255 pub. 9 Jul 92 |
| 146 |  <chem>CCCC1=CN=C(N1Cc2ccc(cc2)N3C=CN(C3)C4=CC=CC=C4F)C</chem> | WO #92/11255 pub. 9 Jul 92 |

TABLE II: Angiotensin II Antagonists

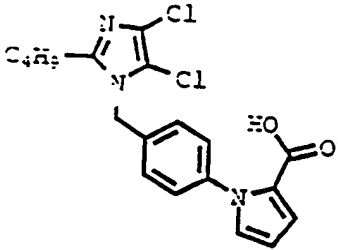
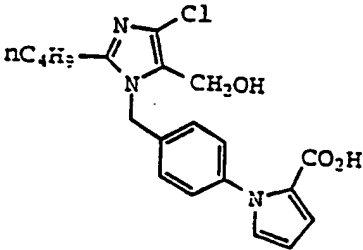
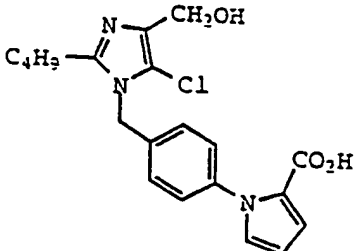
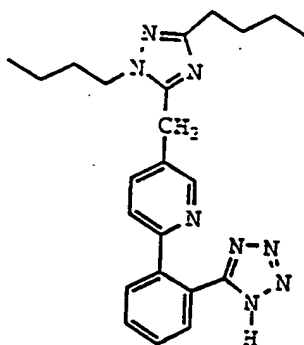
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 147 |  | WO #92/15577 pub. 17 Sep 92 |
| 148 |  | WO #92/15577 pub. 17 Sep 92 |
| 149 |  | WO #92/15577 pub. 17 Sep 92 |

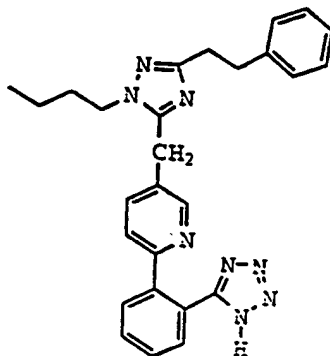
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

150

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151

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152

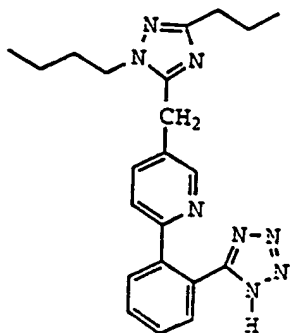
WO #92/16523
pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

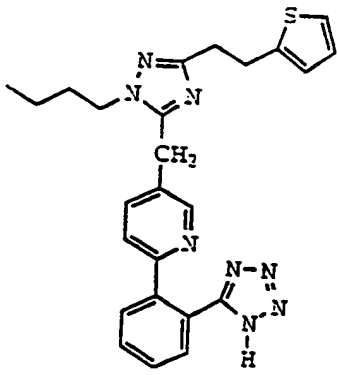
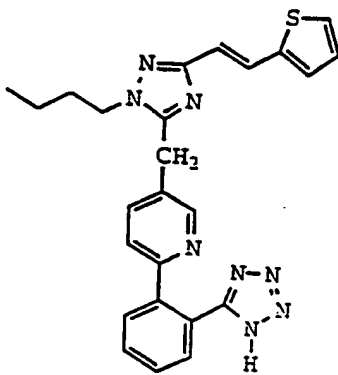
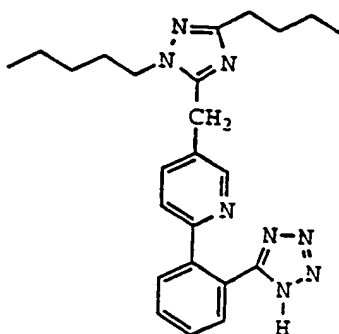
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 153 |  | WO #92/16523 pub. 1 Oct 92 |
| 154 |  | WO #92/16523 pub. 1 Oct 92 |
| 155 |  | WO #92/16523 pub. 1 Oct 92 |

TABLE II: Angiotensin II Antagonists

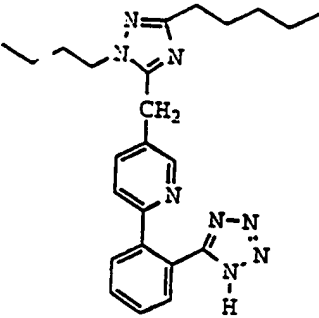
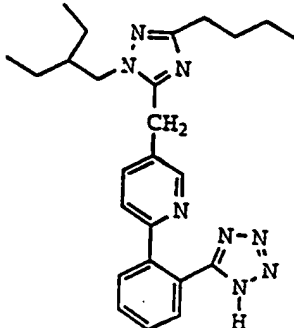
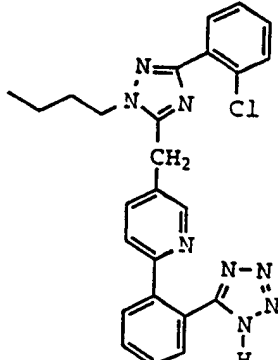
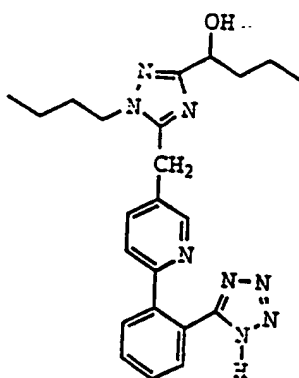
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 156 |  | WO #92/16523 pub. 1 Oct 92 |
| 157 |  | WO #92/16523 pub. 1 Oct 92 |
| 158 |  | WO #92/16523 pub. 1 Oct 92 |

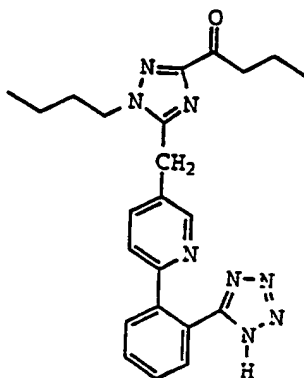
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

159

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pub. 1 Oct 92

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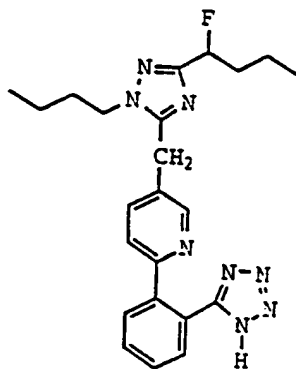
WO #92/16523
pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

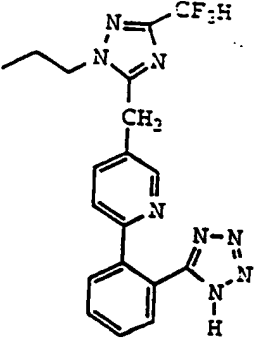
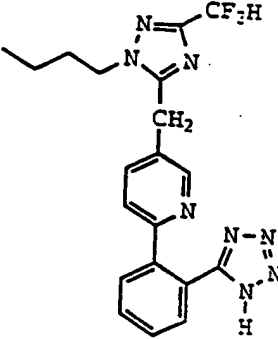
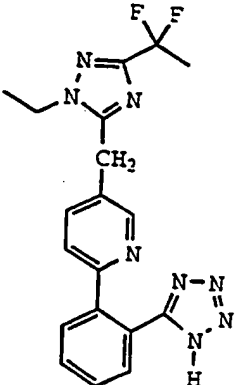
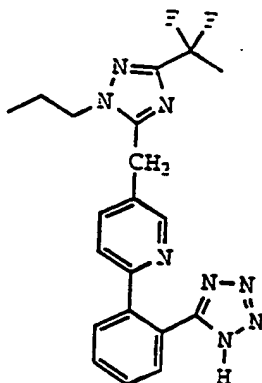
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 162 |  | WO #92/16523 pub. 1 Oct 92 |
| 163 |  | WO #92/16523 pub. 1 Oct 92 |
| 164 |  | WO #92/16523 pub. 1 Oct 92 |

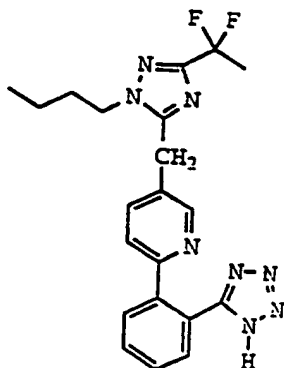
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

165

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166

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167

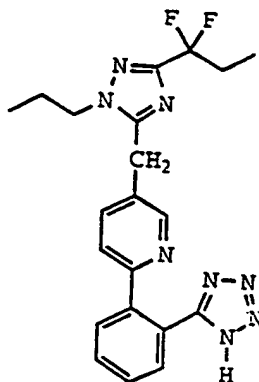
WO #92/16523
pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

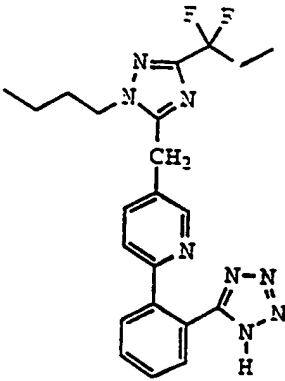
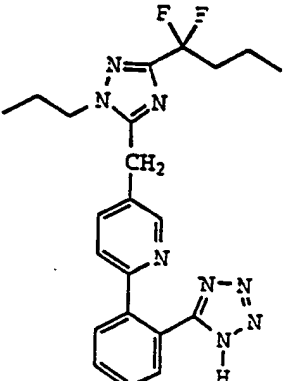
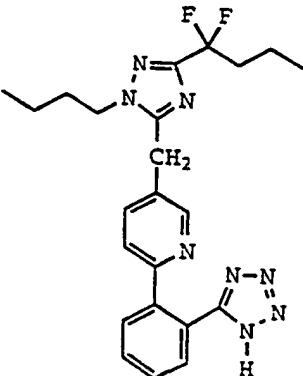
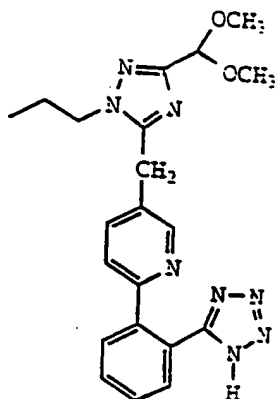
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 168 |  | WO #92/16523 pub. 1 Oct 92 |
| 169 |  | WO #92/16523 pub. 1 Oct 92 |
| 170 |  | WO #92/16523 pub. 1 Oct 92 |

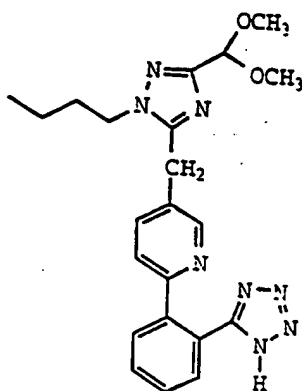
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

174

WO #92/16523
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175

WO #92/16523
pub. 1 Oct 92

176

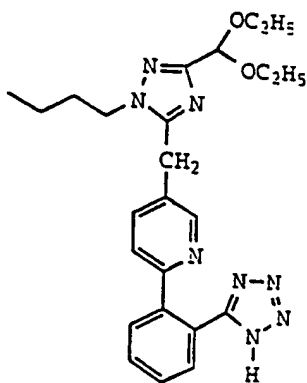
WO #92/16523
pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

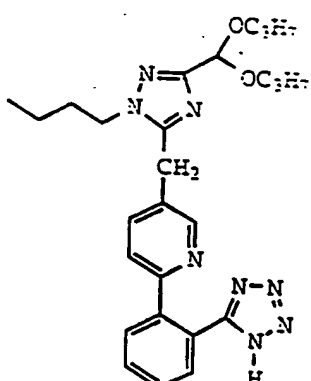
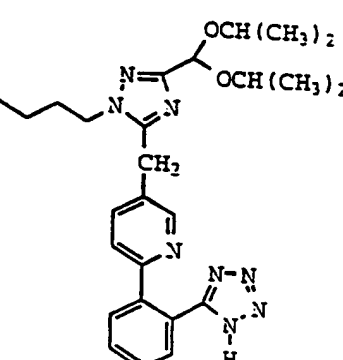
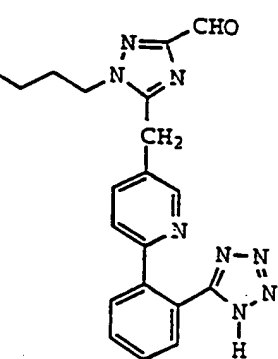
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 177 |  | WO #92/16523 pub. 1 Oct 92 |
| 178 |  | WO #92/16523 pub. 1 Oct 92 |
| 179 |  | WO #92/16523 pub. 1 Oct 92 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|-------------------------------|
| 180 | | WO #92/16523 pub. 1 Oct 92 |
| 181 | | WO #92/16523 pub. 1 Oct 92 |
| 182 | | WO #92/16523 pub. 1 Oct 92 |

TABLE II: Angiotensin II Antagonists

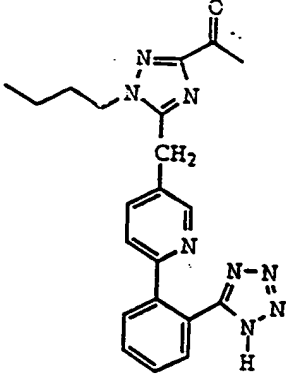
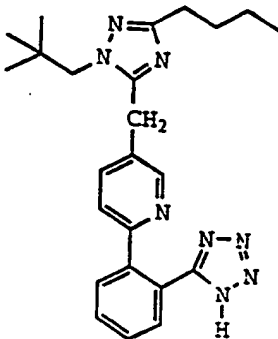
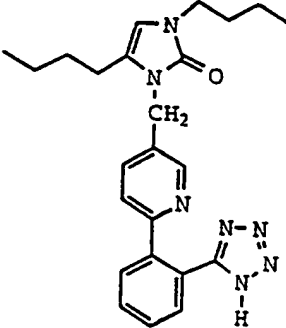
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 183 |  | WO #92/16523 pub. 1 Oct 92 |
| 184 |  | WO #92/16523 pub. 1 Oct 92 |
| 185 |  | WO #92/17469 pub. 15 Oct 92 |

TABLE II: Angiotensin II Antagonists

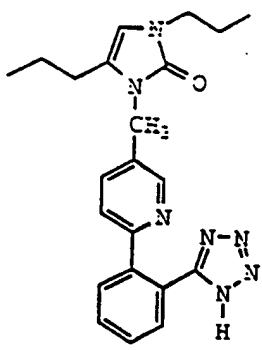
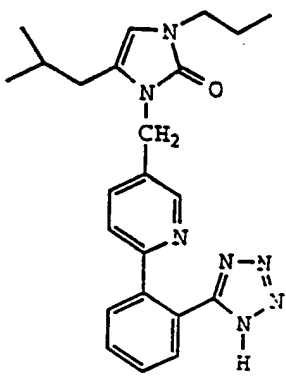
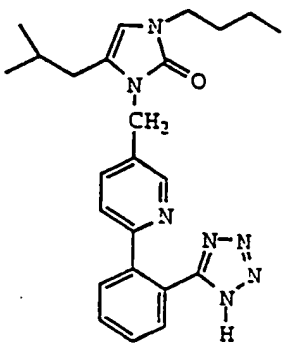
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 186 |  | WO #92/17469 pub. 15 Oct 92 |
| 187 |  | WO #92/17469 pub. 15 Oct 92 |
| 188 |  | WO #92/17469 pub. 15 Oct 92 |

TABLE II: Angiotensin II Antagonists

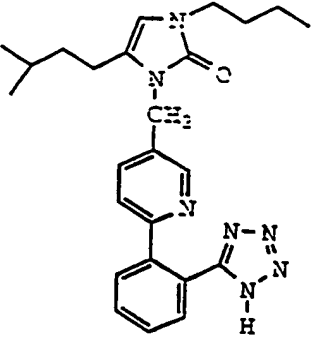
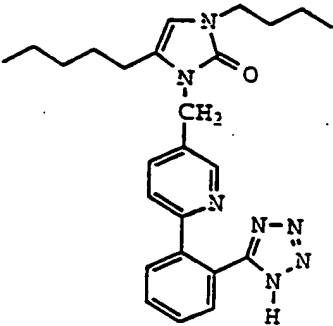
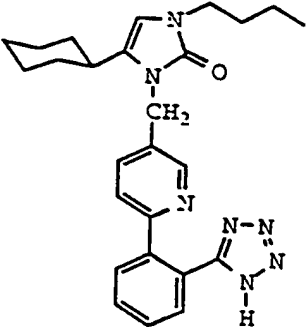
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 189 |  | WO #92/17469 pub. 15 Oct 92 |
| 190 |  | WO #92/17469 pub. 15 Oct 92 |
| 191 |  | WO #92/17469 pub. 15 Oct 92 |

TABLE II: Angiotensin II Antagonists

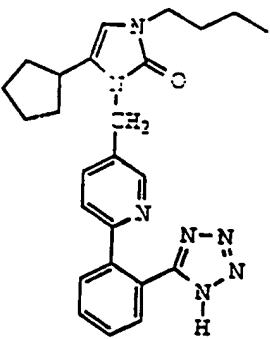
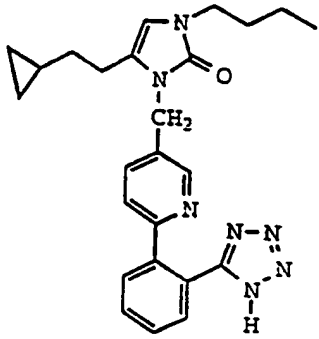
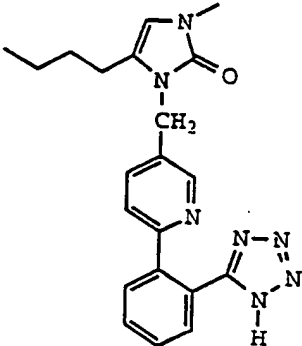
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 192 |  | WO #92/17469 pub. 15 Oct 92 |
| 193 |  | WO #92/17469 pub. 15 Oct 92 |
| 194 |  | WO #92/17469 pub. 15 Oct 92 |

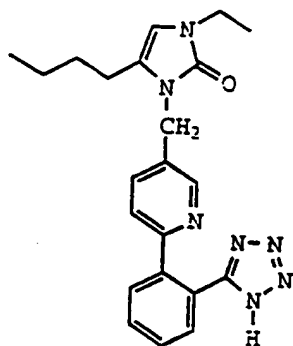
TABLE II: Angiotensin II Antagonists

Compound #

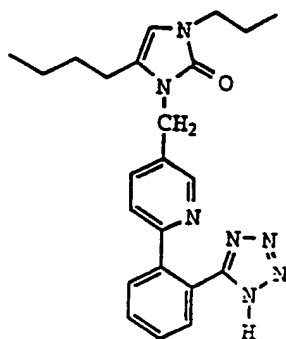
Structure

Source

195

WO #92/17469
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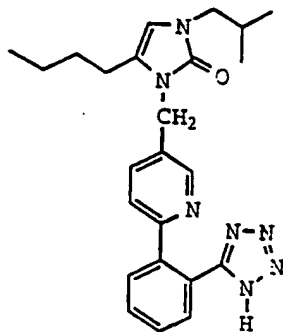
WO #92/17469
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TABLE II: Angiotensin II Antagonists

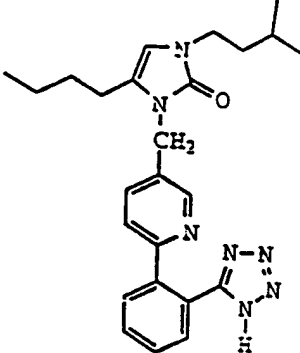
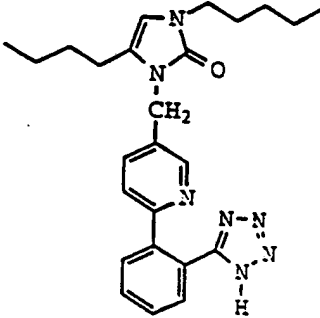
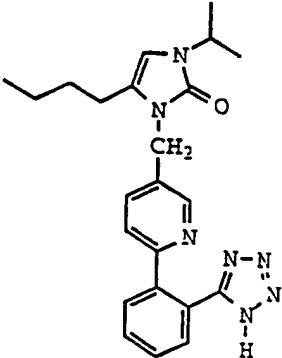
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 198 |  | WO #92/17469 pub. 15 Oct 92 |
| 199 |  | WO #92/17469 pub. 15 Oct 92 |
| 200 |  | WO #92/17469 pub. 15 Oct 92 |

TABLE II: Angiotensin II Antagonists

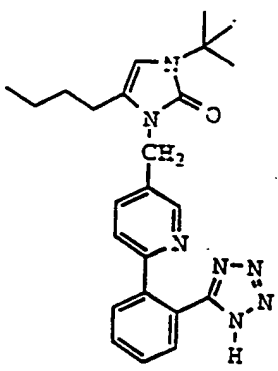
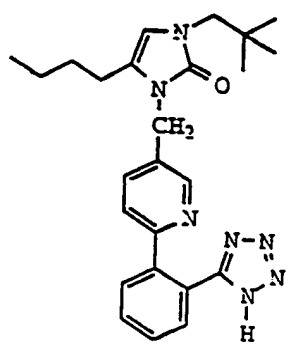
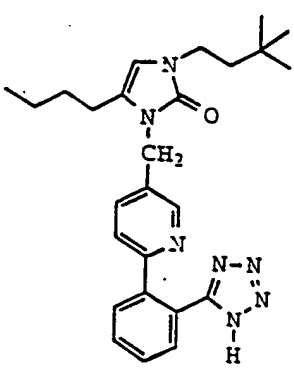
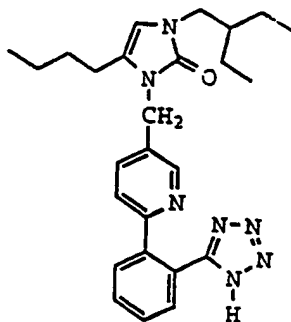
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|------------|---|--------------------------------|
| 201 |  | WO #92/17469 pub. 15 Oct 92 |
| 202 |  | WO #92/17469 pub. 15 Oct 92 |
| 203 |  | WO #92/17469 pub. 15 Oct 92 |

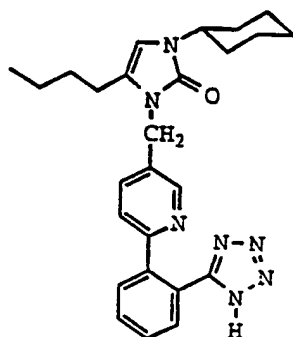
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
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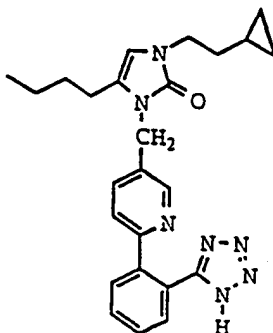
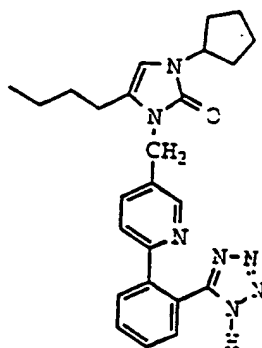
WO #92/17469
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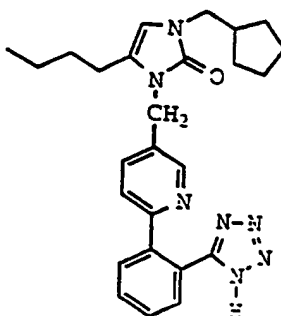
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
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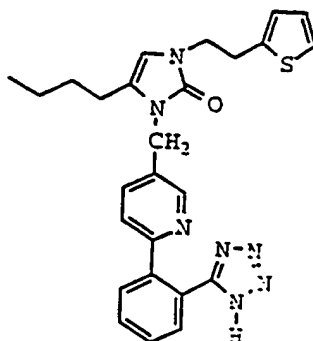
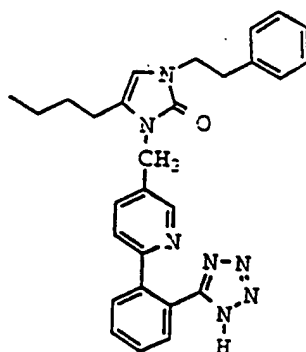
WO #92/17469
pub. 15 Oct 92

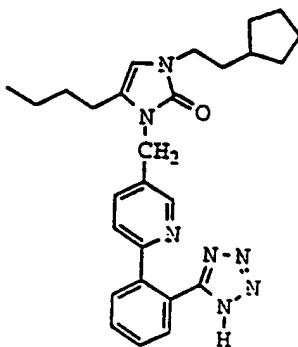
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
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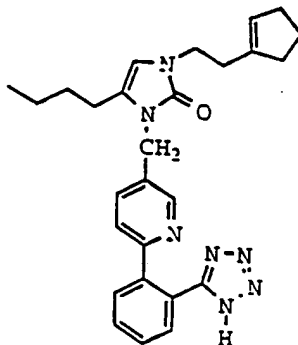
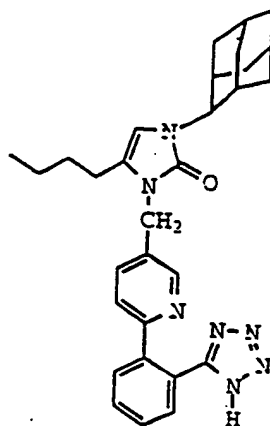
WO #92/17469
pub. 15 Oct 92

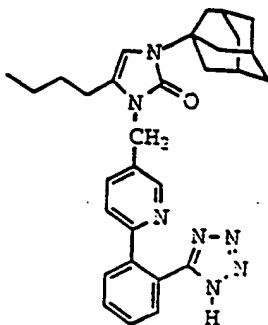
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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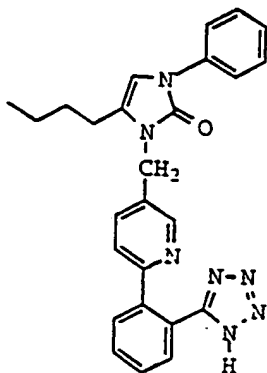
WO #92/17469
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TABLE II: Angiotensin II Antagonists

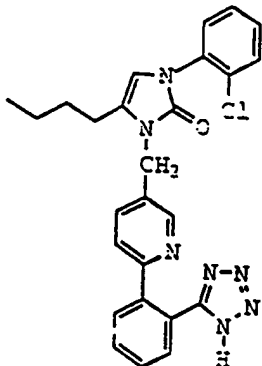
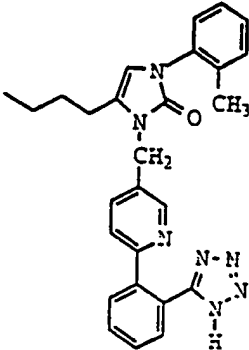
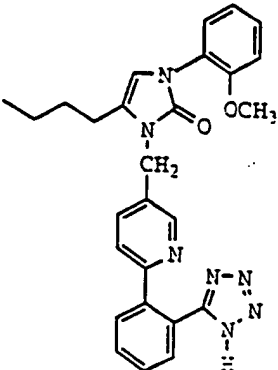
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 216 |  | WO #92/17469 pub. 15 Oct 92 |
| 217 |  | WO #92/17469 pub. 15 Oct 92 |
| 218 |  | WO #92/17469 pub. 15 Oct 92 |

TABLE II: Angiotensin II Antagonists

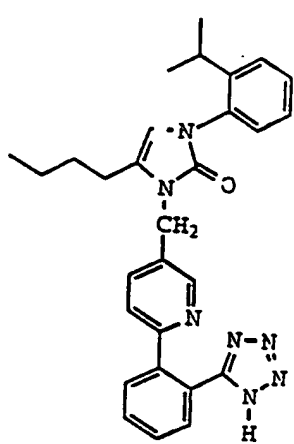
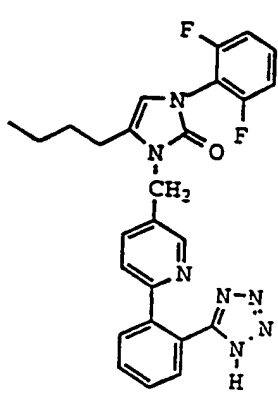
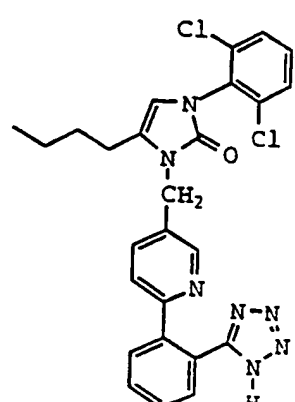
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 219 |  | WO #92/17469 pub. 15 Oct 92 |
| 220 |  | WO #92/17469 pub. 15 Oct 92 |
| 221 |  | WO #92/17469 pub. 15 Oct 92 |

TABLE II: Angiotensin II Antagonists

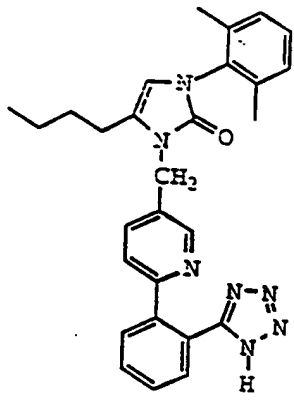
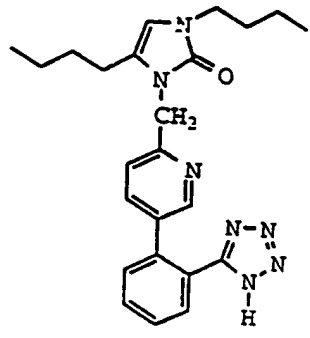
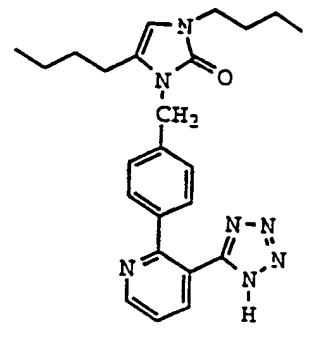
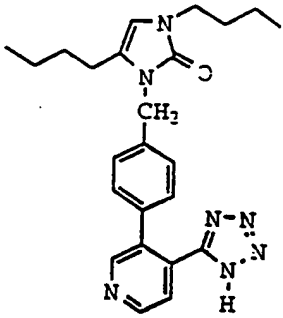
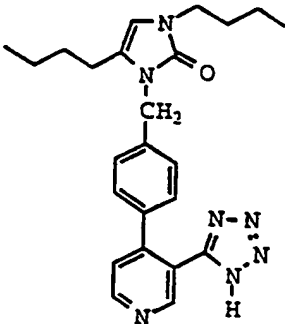
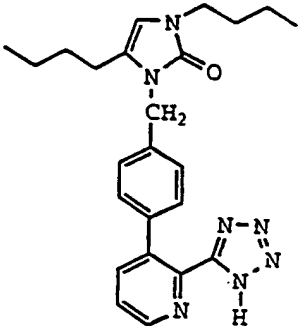
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 222 |  | WO #92/17469 pub. 15 Oct 92 |
| 223 |  | WO #92/17469 pub. 15 Oct 92 |
| 224 |  | WO #92/17469 pub. 15 Oct 92 |

TABLE II: Angiotensin II Antagonists

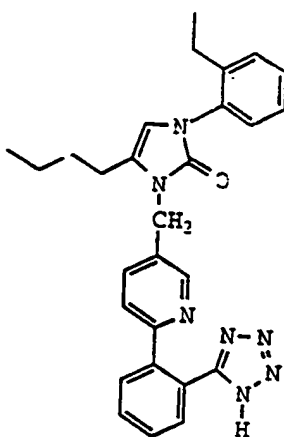
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 225 |  | WO #92/17469 pub. 15 Oct 92 |
| 226 |  | WO #92/17469 pub. 15 Oct 92 |
| 227 |  | WO #92/17469 pub. 15 Oct 92 |

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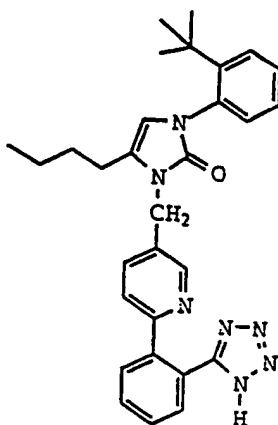
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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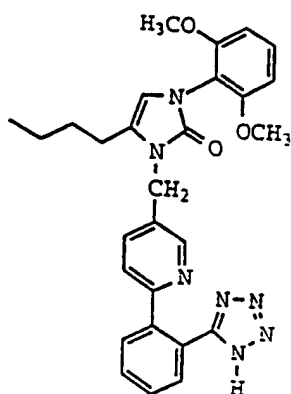
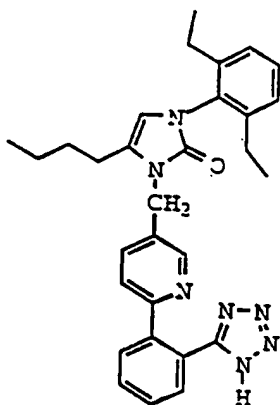


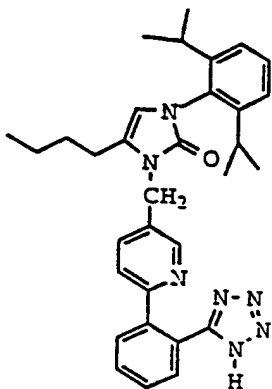
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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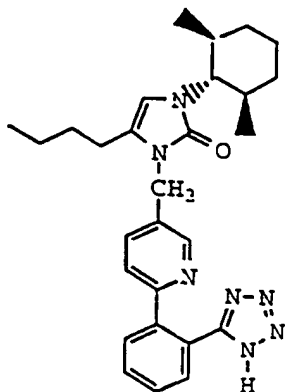
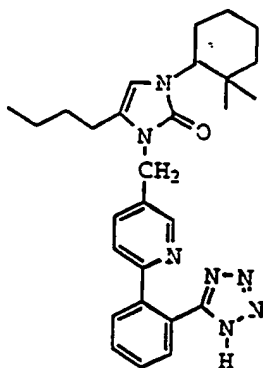


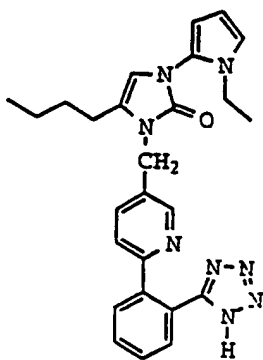
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

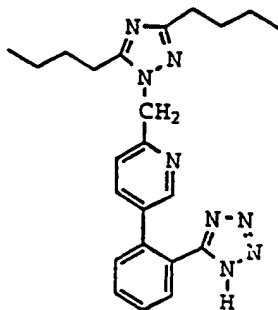
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TABLE II: Angiotensin II Antagonists

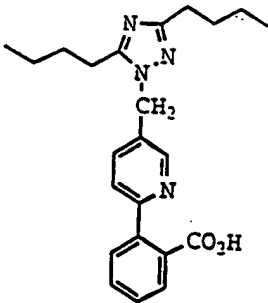
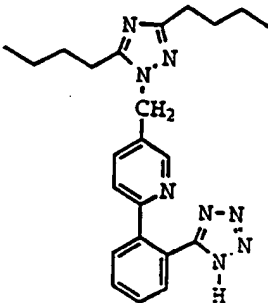
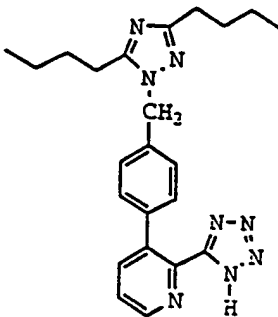
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 240 |  | WO #92/18092 pub. 29 Oct 92 |
| 241 |  | WO #92/18092 pub. 29 Oct 92 |
| 242 |  | WO #92/18092 pub. 29 Oct 92 |

TABLE II: Angiotensin II Antagonists

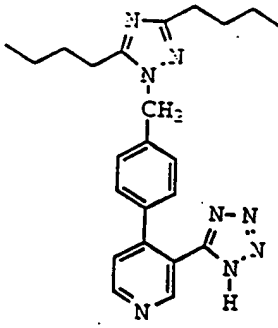
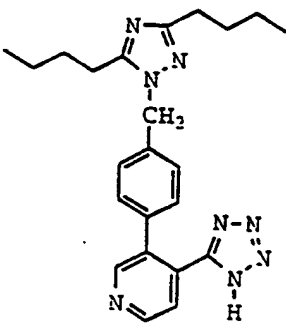
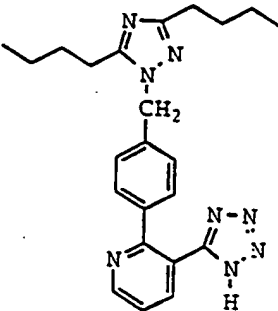
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|------------|---|--------------------------------|
| 243 |  | WO #92/18092 pub. 29 Oct 92 |
| 244 |  | WO #92/18092 pub. 29 Oct 92 |
| 245 |  | WO #92/18092 pub. 29 Oct 92 |

TABLE II: Angiotensin II Antagonists

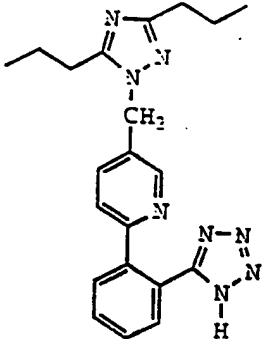
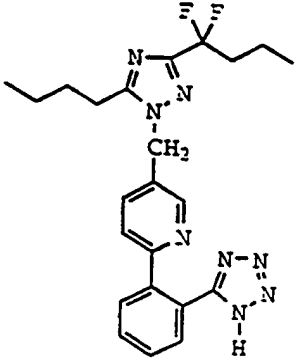
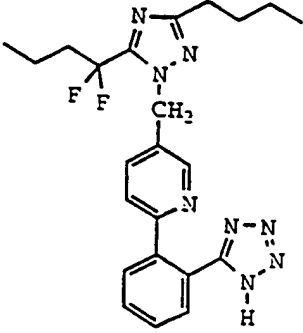
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|------------|---|--------------------------------|
| 246 |  | WO #92/18092 pub. 29 Oct 92 |
| 247 |  | WO #92/18092 pub. 29 Oct 92 |
| 248 |  | WO #92/18092 pub. 29 Oct 92 |

TABLE II: Angiotensin II Antagonists

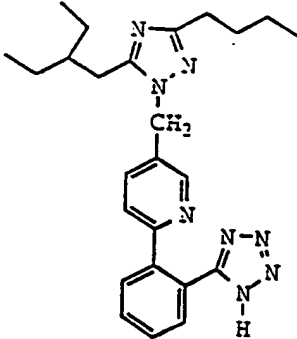
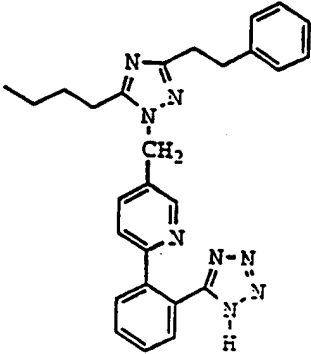
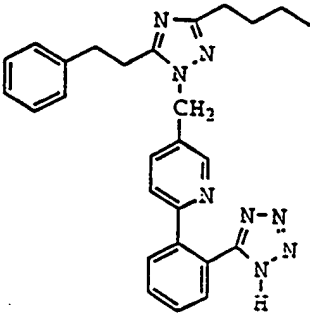
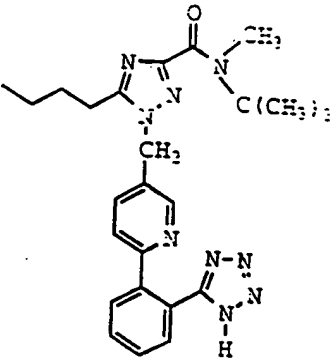
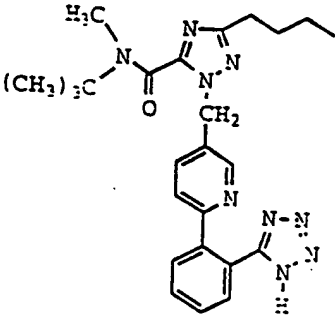
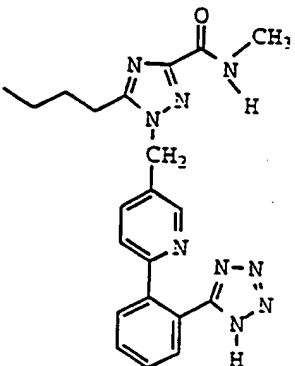
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| 252 |  | WO #92/18092 pub. 29 Oct 92 |
| 253 |  | WO #92/18092 pub. 29 Oct 92 |
| 254 |  | WO #92/18092 pub. 29 Oct 92 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 255 |  | WO #92/18092 pub. 29 Oct 92 |
| 256 |  | WO #92/18092 pub. 29 Oct 92 |
| 257 |  | WO #92/18092 pub. 29 Oct 92 |

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TABLE II: Angiotensin II Antagonists

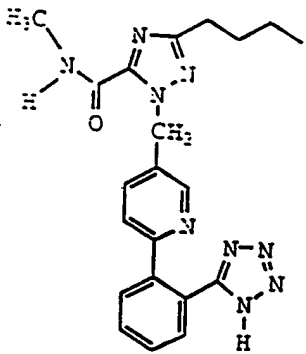
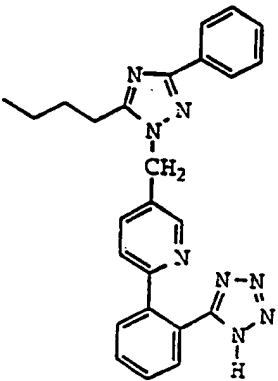
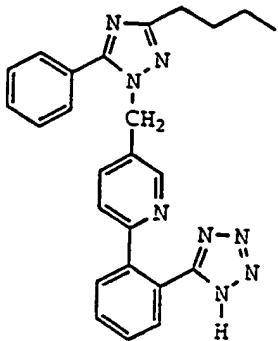
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|------------|---|--------------------------------|
| 258 |  | WO #92/18092 pub. 29 Oct 92 |
| 259 |  | WO #92/18092 pub. 29 Oct 92 |
| 260 |  | WO #92/18092 pub. 29 Oct 92 |

TABLE II: Angiotensin II Antagonists

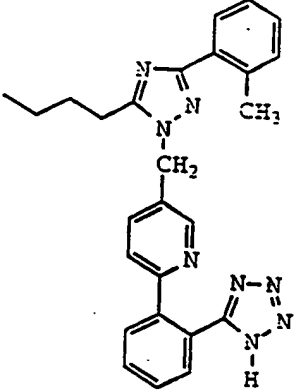
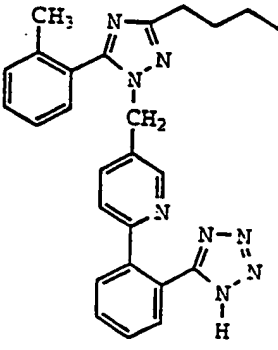
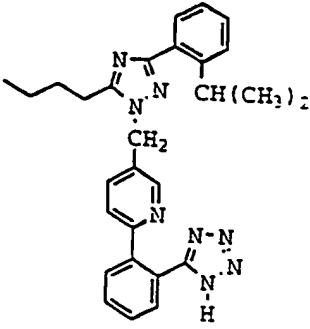
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|------------|---|--------------------------------|
| 261 |  | WO #92/18092 pub. 29 Oct 92 |
| 262 |  | WO #92/18092 pub. 29 Oct 92 |
| 263 |  | WO #92/18092 pub. 29 Oct 92 |

TABLE II: Angiotensin II Antagonists

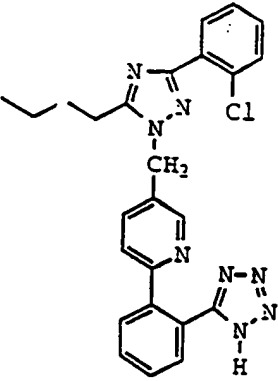
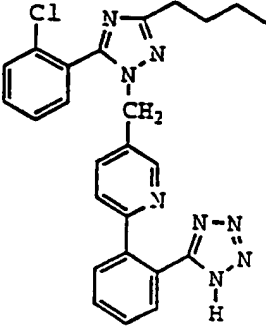
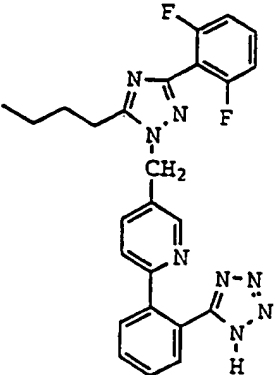
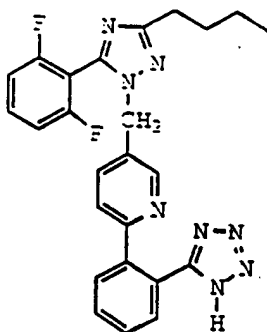
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 267 |  | WO #92/18092 pub. 29 Oct 92 |
| 268 |  | WO #92/18092 pub. 29 Oct 92 |
| 269 |  | WO #92/18092 pub. 29 Oct 92 |

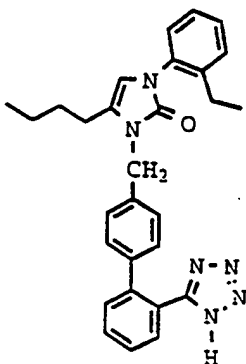
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
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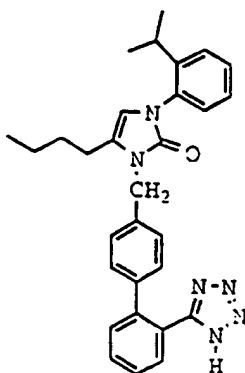
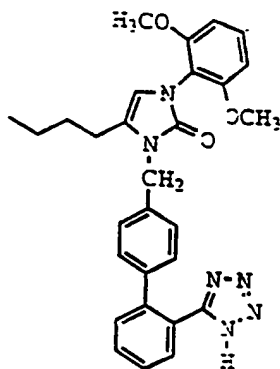
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filed 8 Mar 94

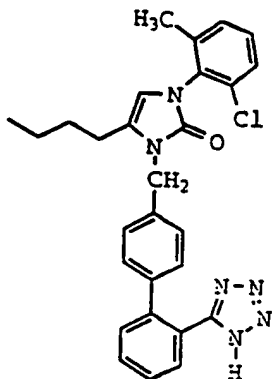
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
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PCT/US94/02156
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PCT/US94/02156
filed 8 Mar 94

275

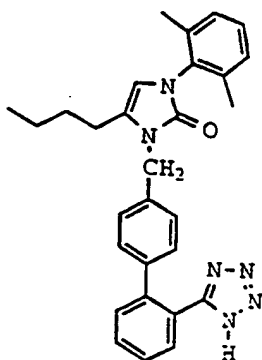
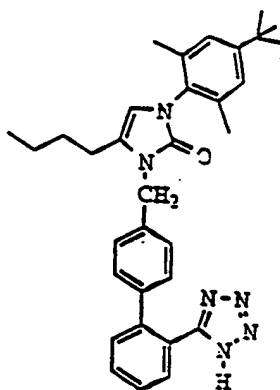
PCT/US94/02156
filed 8 Mar 94

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

279

PCT/US94/02156
filed 8 Mar 94

280

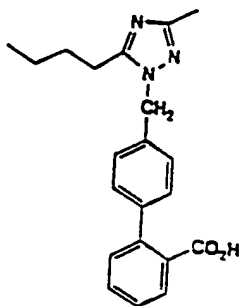
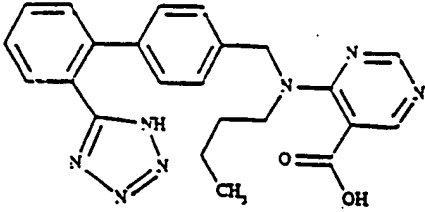
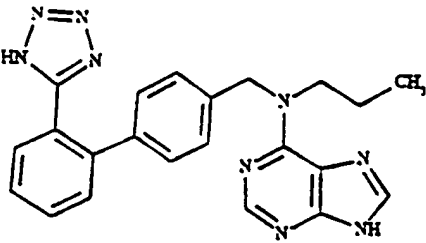
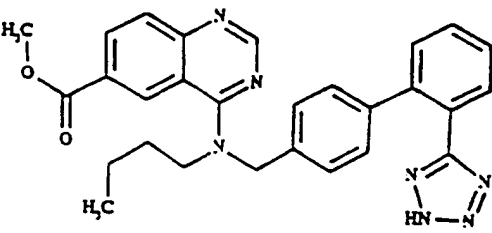
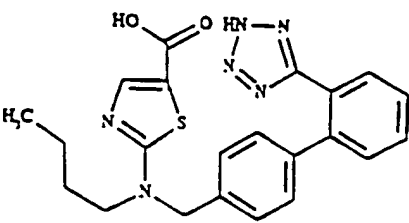
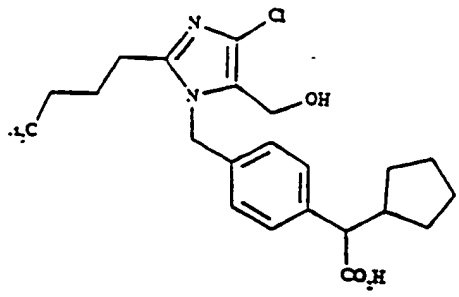
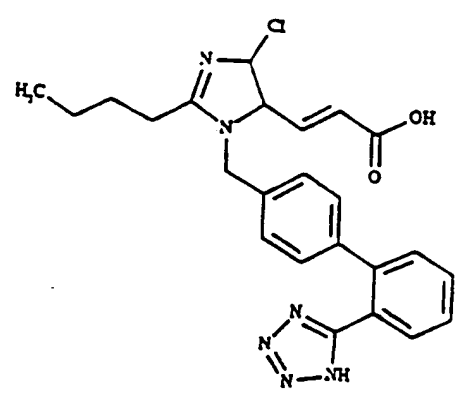
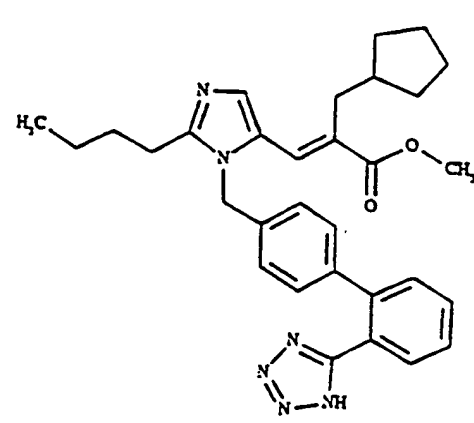
WO #91/17148
pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|--|--------------------------------|
| 281 |  | EP #475,206 pub. 18 Mar 92 |
| 282 |  | WO #93/18035 pub. 16 Sep 93 |
| 283 |  | WO #93/17628 pub. 16 Sep 93 |
| 284 |  | WO #93/17681 pub. 16 Sep 93 |

120

TABLE II: Angiotensin II Antagonists

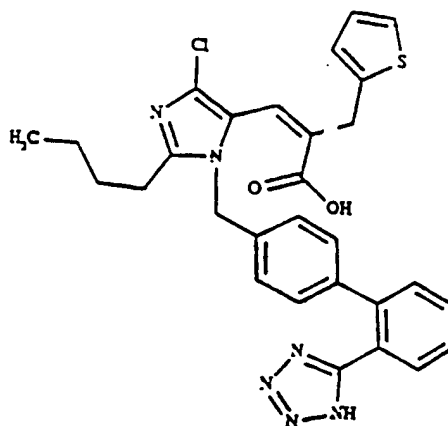
| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 285 |  | EP #513,533 pub. 19 Nov 92 |
| 286 |  | EP #535,463 pub. 07 Apr 93 |
| 287 |  | EP #535,465 pub. 07 Apr 93 |

121

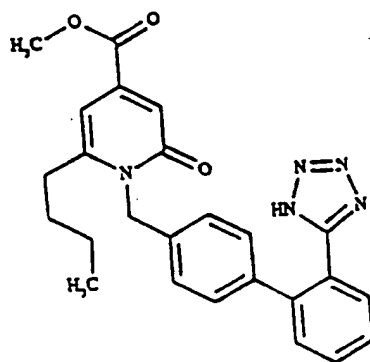
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

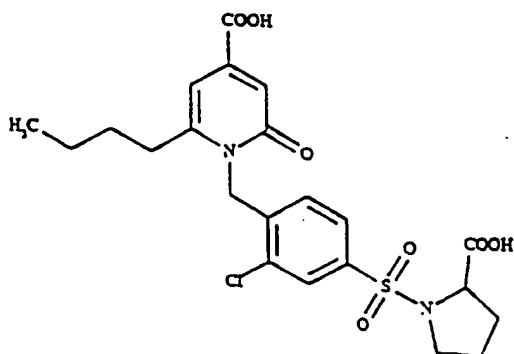
288

EP #539,713
pub. 05 May 93

289

EP #542,059
pub. 19 May 93

290

EP #05 557,843
pub. 01 Sep 93

122

TABLE II: Angiotensin II Antagonists

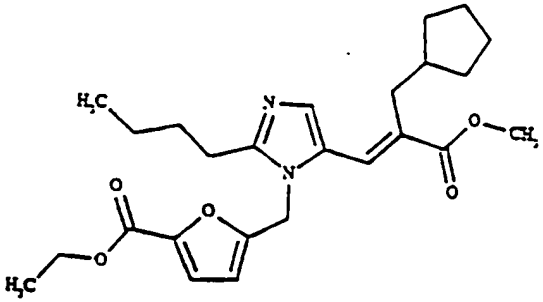
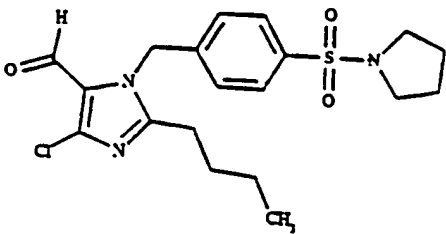
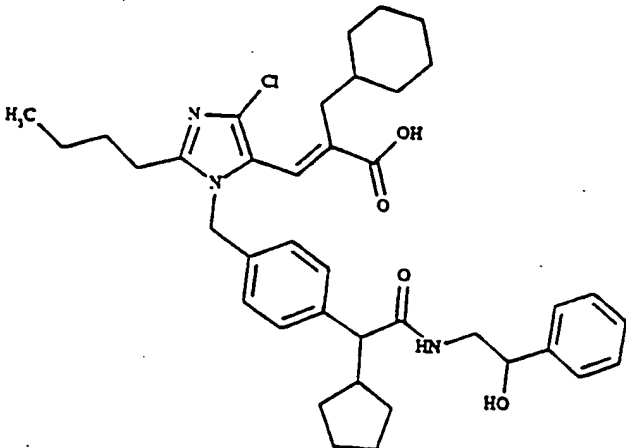
| Compound # | Structure | Source |
|------------|--|----------------------------------|
| 291 |  | EP #563,705 pub. 06 Oct 93 |
| 292 |  | EP #562,261 pub. 29 Sep 93 |
| 293 |  | EP #05 557,843 pub. 15 Sep 93 |

TABLE II: Angiotensin II Antagonists

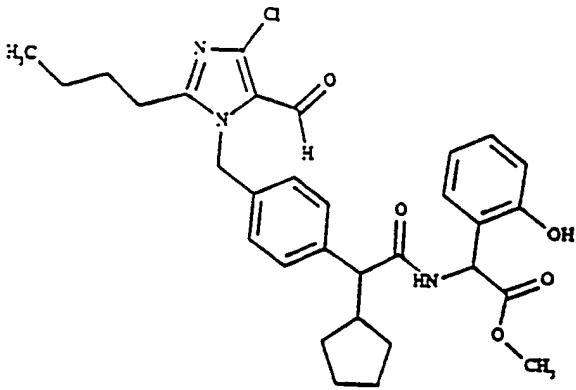
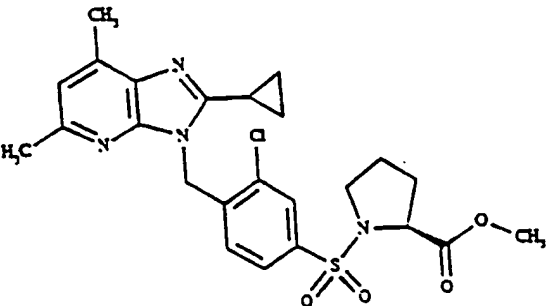
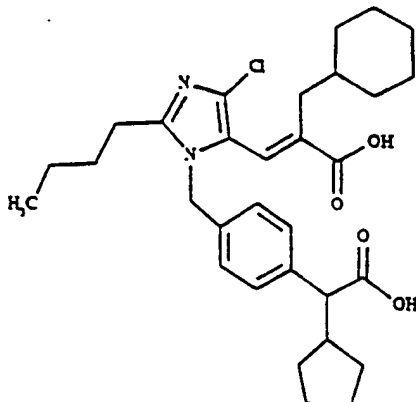
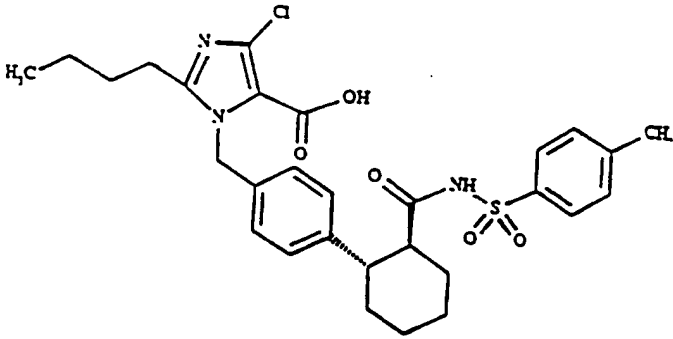
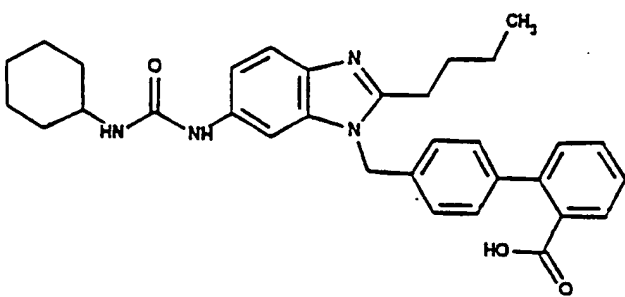
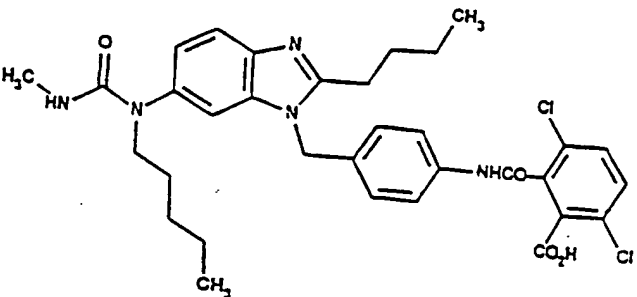
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 294 |  | EP #560,163 pub. 15 Sep 93 |
| 295 |  | EP #564, 788 pub. 13 Oct 93 |
| 296 |  | EP #563,986 pub. 20 Oct 93 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|---------------------------------|
| 297 | | EP #0,569,795 pub. 18 Nov 93 |
| 298 | | EP #0,569,794 pub. 18 Nov 93 |
| 299 | | EP #0,578,002 pub. 12 Jan 94 |

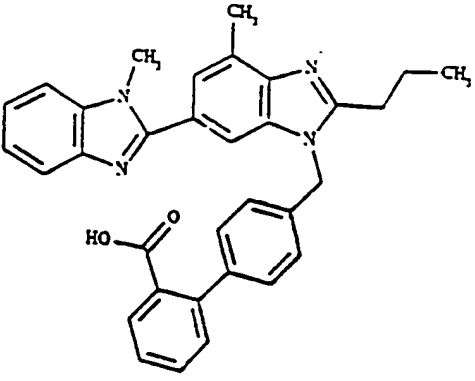
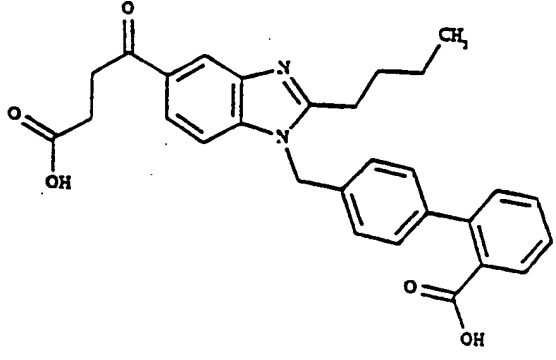
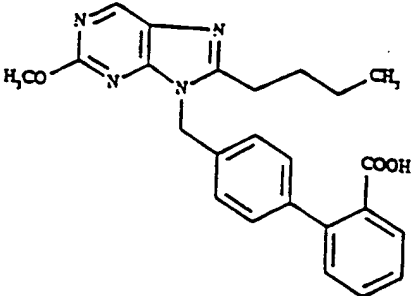
125

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 300 |  | EP #581,003 pub. 02 Feb 94 |
| 301 |  | EP #392,317 pub. 17 Oct 90 |
| 302 |  | EP #392,317 pub. 17 Oct 90 |

126

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 303 |  | EP #502,314 pub. 09 Sep 92 |
| 304 |  | EP #468,740 pub. 29 Jan 92 |
| 305 |  | EP #470,543 pub. 12 Feb 92 |

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TABLE II: Angiotensin II Antagonists

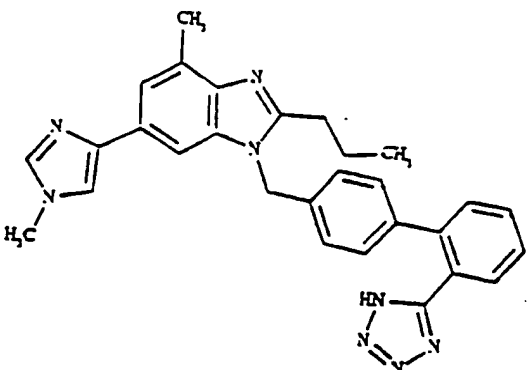
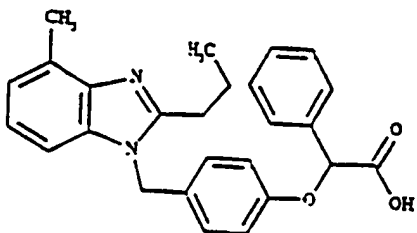
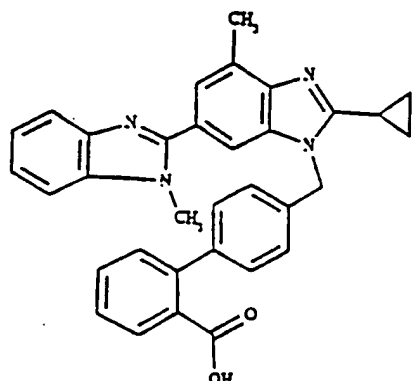
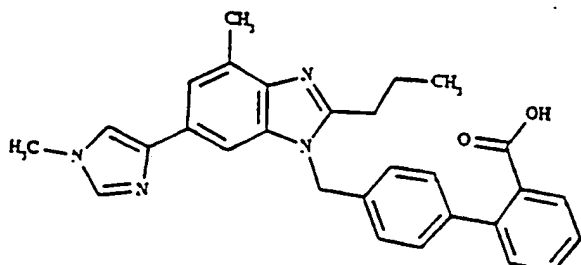
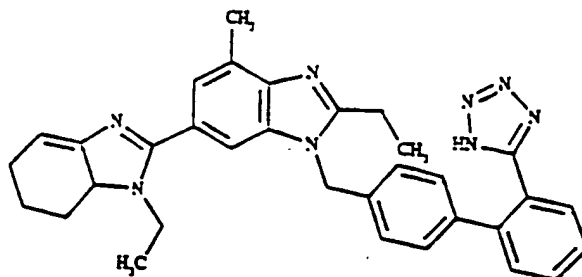
| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 306 |  | EP #502,314 pub. 09 Sep 92 |
| 307 |  | EP #529,253 pub. 03 Mar 93 |
| 308 |  | EP #543,263 pub. 26 May 93 |
| 309 |  | EP #552,765 pub. 28 Jul 93 |

TABLE II: Angiotensin II Antagonists

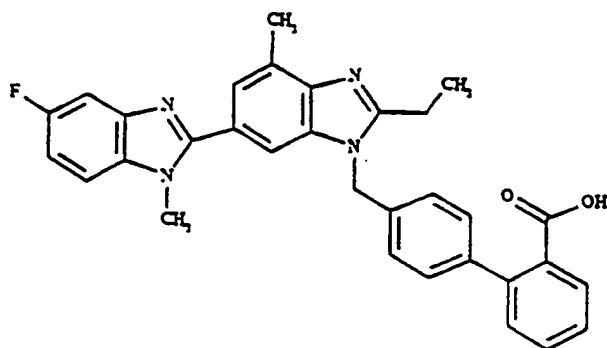
| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

313



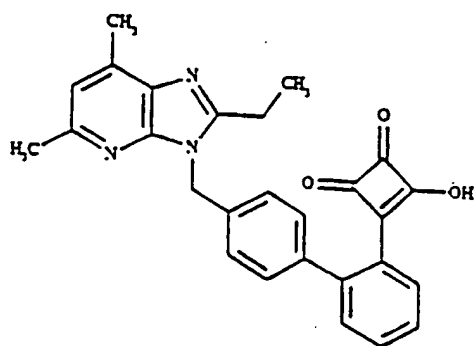
EP #566,020
pub. 20 Oct 93

314



EP #581,166
pub. 02 Feb 94

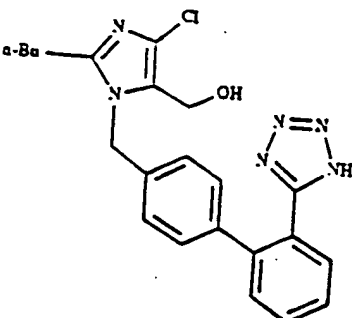
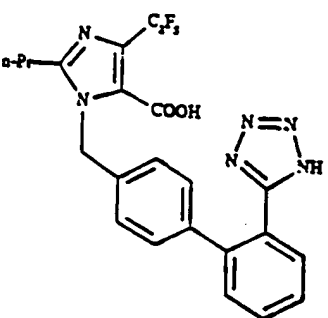
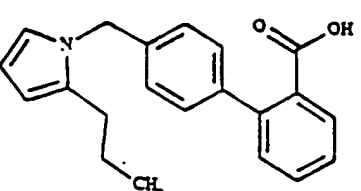
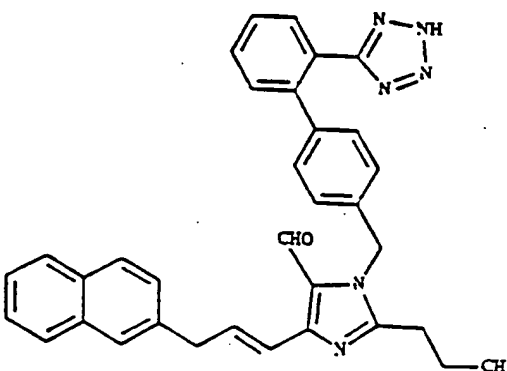
315



WO #94/01436
pub. 20 Jan 94

130

TABLE II: Angiotensin II Antagonists

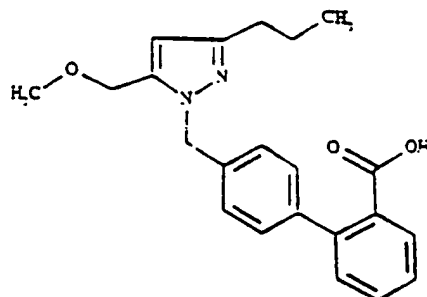
| Compound # | Structure | Source |
|------------|--|-----------------------------------|
| 316 |  | EP #253,310 pub. 20 Jan 88 |
| 317 |  | EP #324,377 pub. 19 Jul 89 |
| 318 |  | US #5,043,349 issued 27 Aug 91 |
| 319 |  | WO #91/00281 pub. 10 Jan 91 |

131

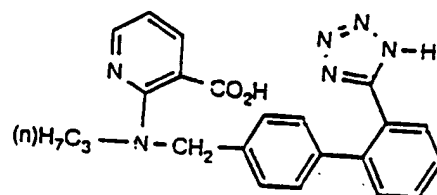
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

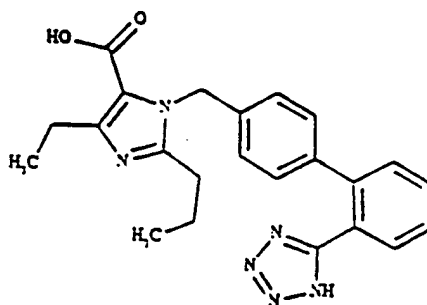
320

US #5,015,651
pub. 14 May 91

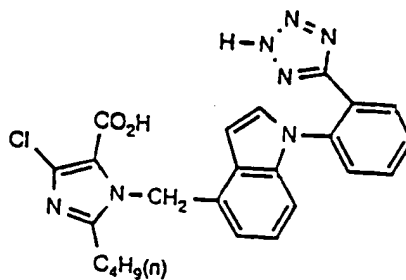
321



322

WO #92/00977
pub. 23 Jan 92

323

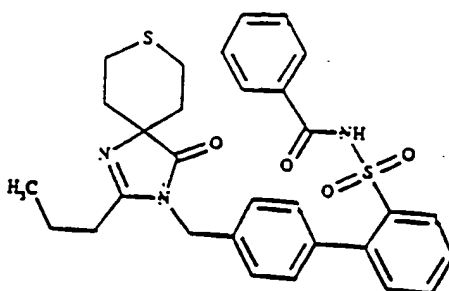


132

TABLE II: Angiotensin II Antagonists

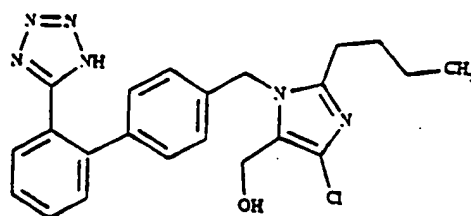
| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

324



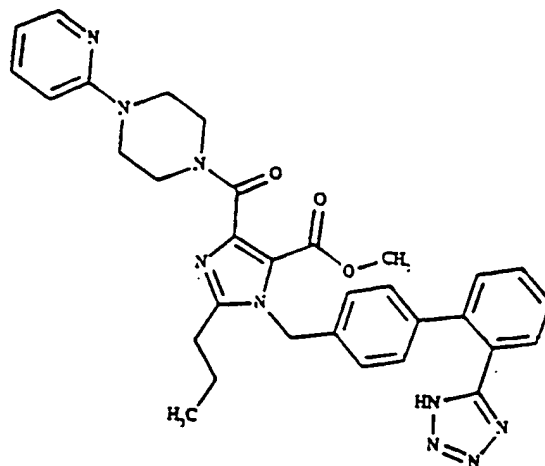
WO #93/04046
pub. 04 Mar 93

325



WO #93/10106
pub. 27 May 93

326



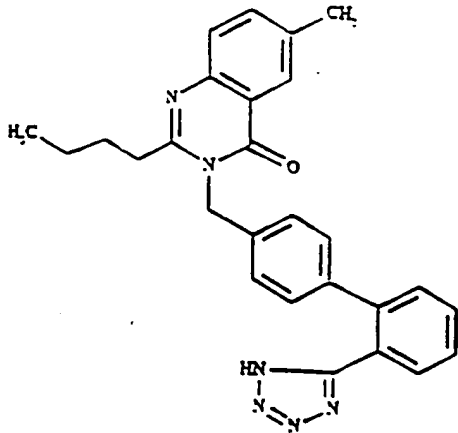
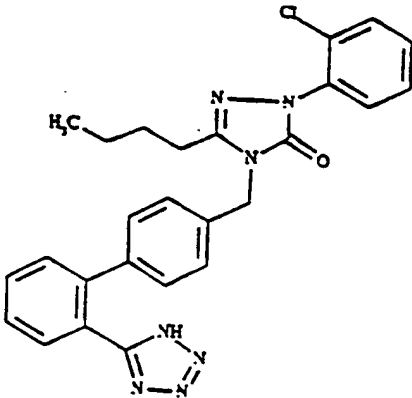
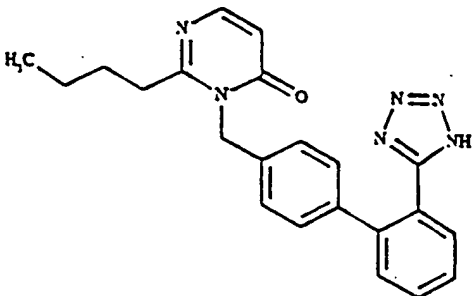
US #5,219,856
pub. 15 Jun 93

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|---------------------------------|
| 327 | | US #5,260,325 pub. 09 Nov 93 |
| 328 | | US #5,264,581 pub. 23 Nov 93 |
| 329 | | EP #400,974 pub. 05 Dec 90 |

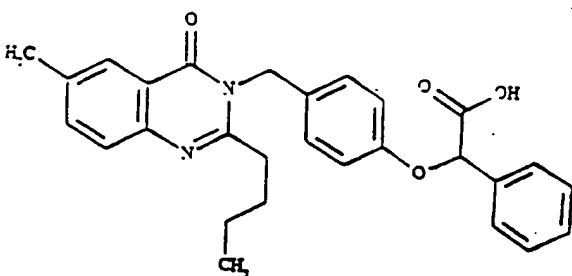
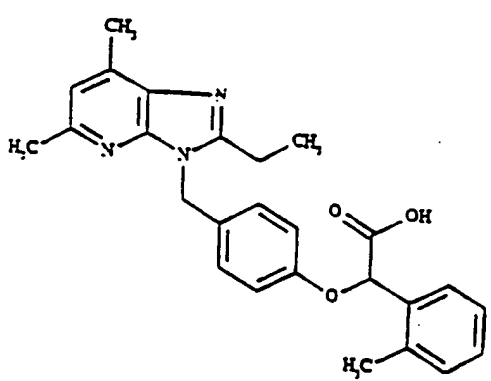
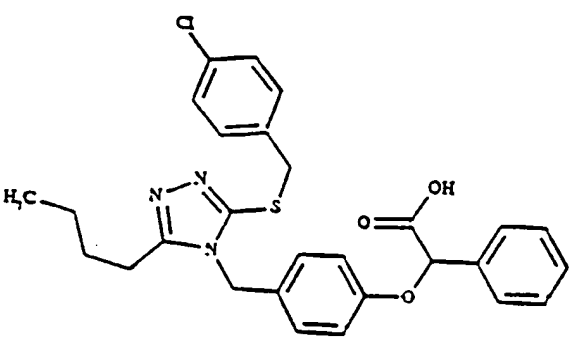
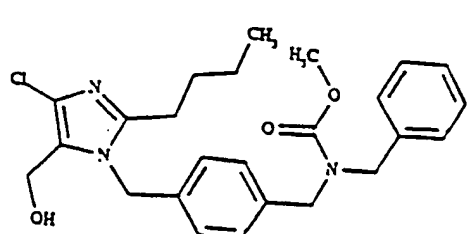
134

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 330 |  | EP #411,766 pub. 06 Feb 91 |
| 331 |  | EP #412,594 pub. 13 Feb 91 |
| 332 |  | EP #419,048 pub. 27 Mar 91 |

135

TABLE II: Angiotensin II Antagonists

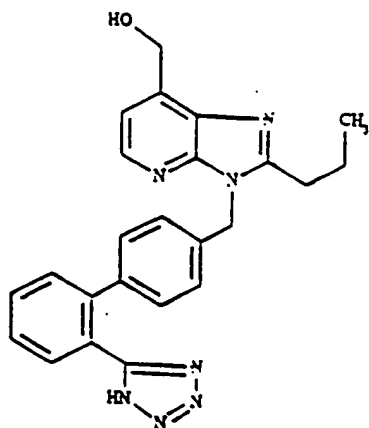
| Compound # | Structure | Source |
|------------|--|---------------------------------|
| 333 |  | WO #91/12,001 pub. 22 Aug 91 |
| 334 |  | WO #91/11,999 pub. 22 Aug 91 |
| 335 |  | WO #91/11,909 pub. 22 Aug 91 |
| 336 |  | WO #91/12,002 pub. 22 Aug 91 |

136

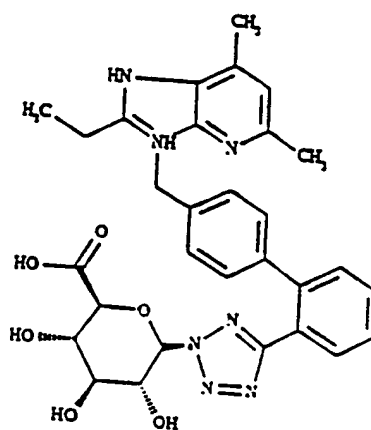
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

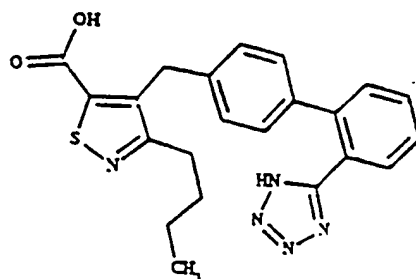
337

US #5,053,329
pub. 01 Oct 91

338

US #5,057,522
pub 15 Oct 91

339

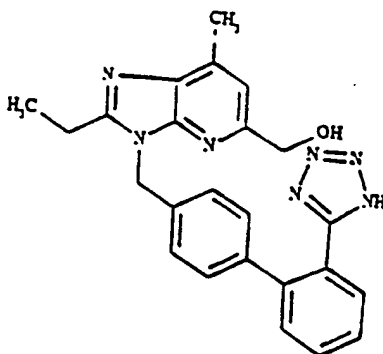
WO #91/15,479
pub. 17 Oct 91

137

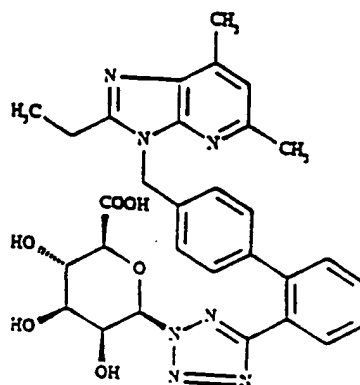
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

340

EP #456,510
pub. 13 Nov 91

341

EP #467,715
pub. 22 Jan 92

342

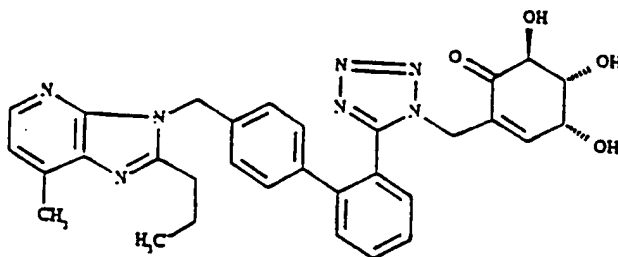
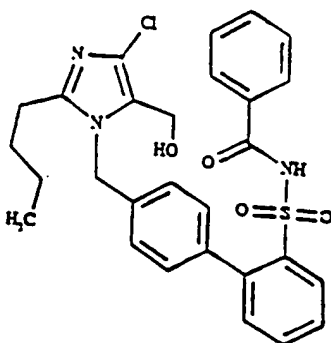
US #5,087,702
pub. 11 Feb 92

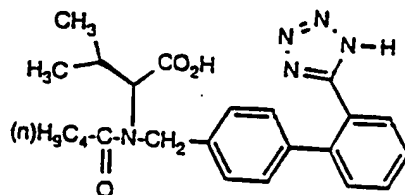
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

343

EP #479,479
pub. 08 Apr 92

344



345

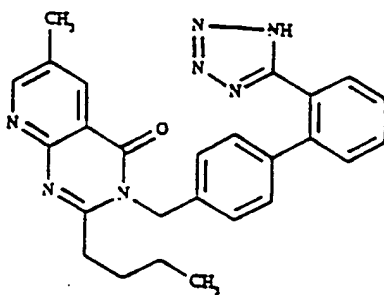
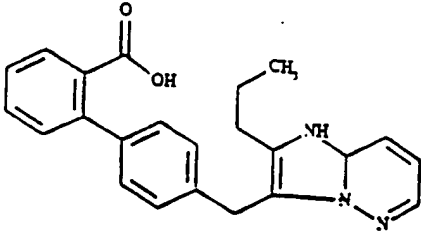
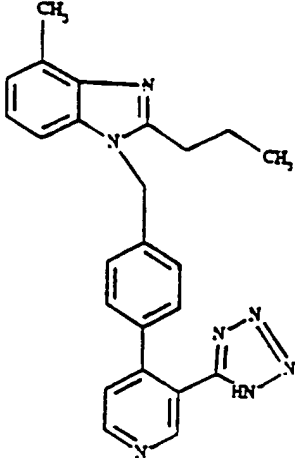
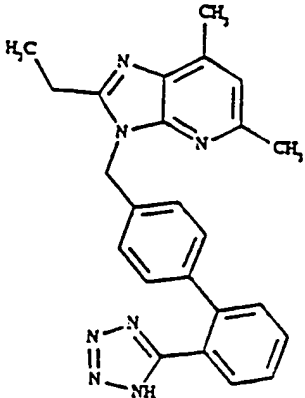
EP #481,614
pub. 22 Apr 92

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|---|---------------------------------|
| 346 |  | EP #490,587 pub. 17 Jun 92 |
| 347 |  | US #5,128,327 pub. 07 Jul 92 |
| 348 |  | US #5,132,216 pub. 21 Jul 92 |

140

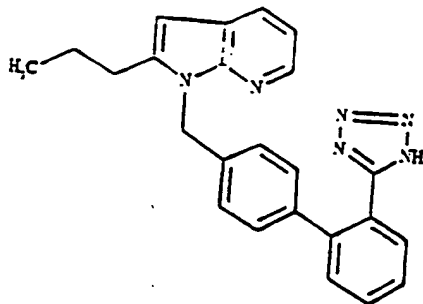
TABLE II: Angiotensin II Antagonists

Compound #

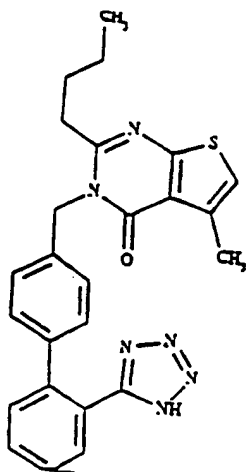
Structure

Source

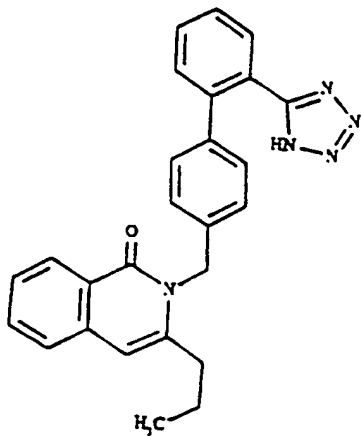
349

EP #497,516
pub. 05 Aug 92

350

EP #502,725
pub. 09 Sep 92

351

EP #502,575
pub. 09 Sep 92

141

TABLE II: Angiotensin II Antagonists

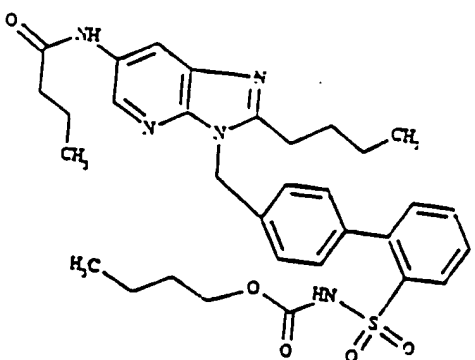
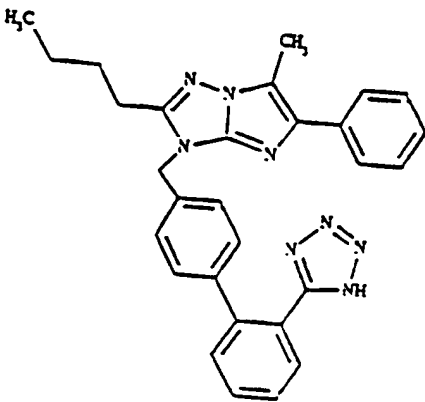
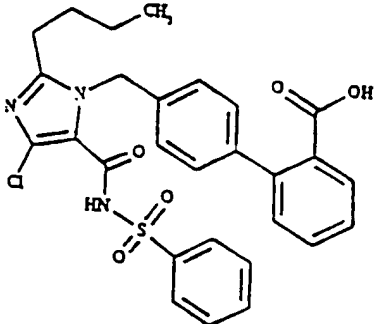
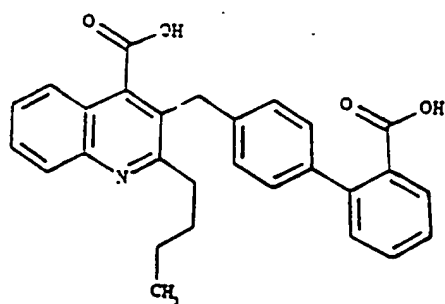
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 352 |  | EP #503,838 pub. 16 Sep 92 |
| 353 |  | EP #505,111 pub. 23 Sep 92 |
| 354 |  | EP #505,098 pub. 23 Sep 92 |

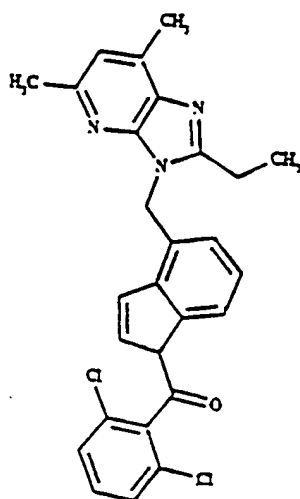
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

355

EP #507,594
pub. 37 Oct 92

356

EP #508,723
pub. 14 Oct 92

357

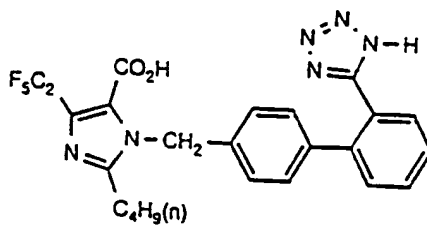


TABLE II: Angiotensin II Antagonists

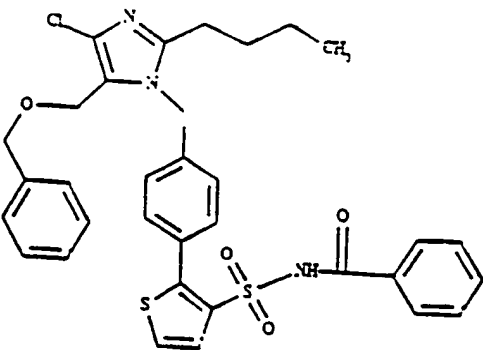
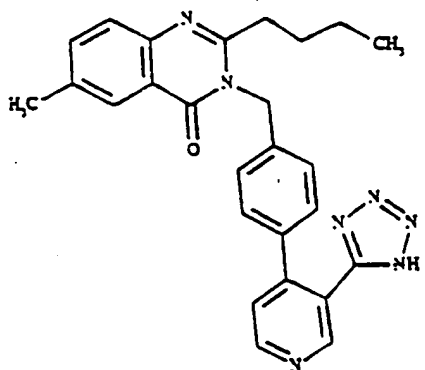
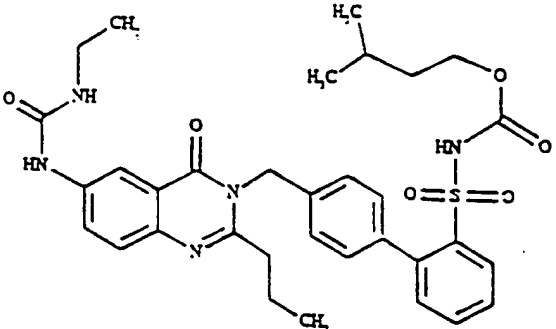
| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 358 |  | EP #512,675 pub. 11 Nov 92 |
| 359 |  | EP #512,676 pub. 11 Nov 92 |
| 360 |  | EP #512,370 pub. 11 Nov 92 |

TABLE II: Angiotensin II Antagonists

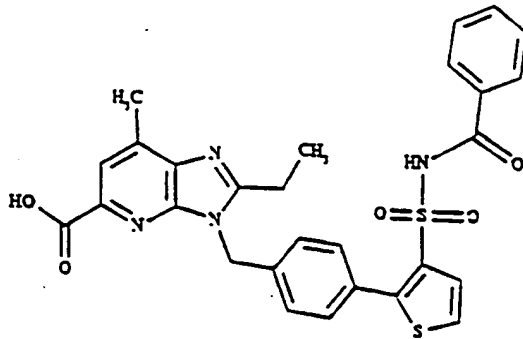
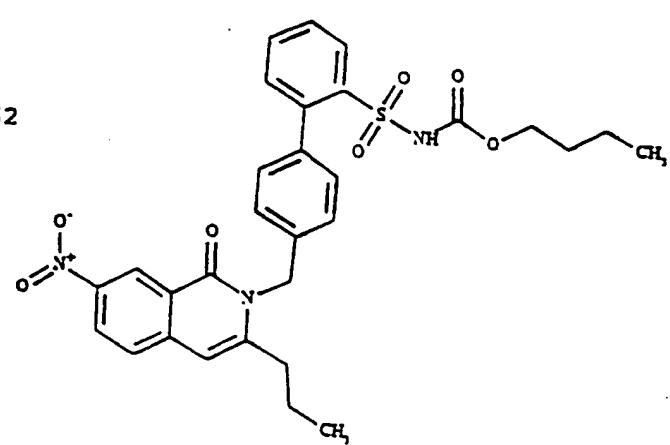
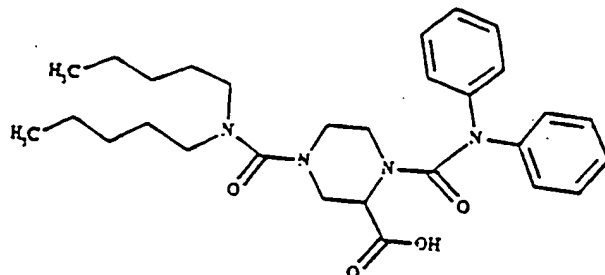
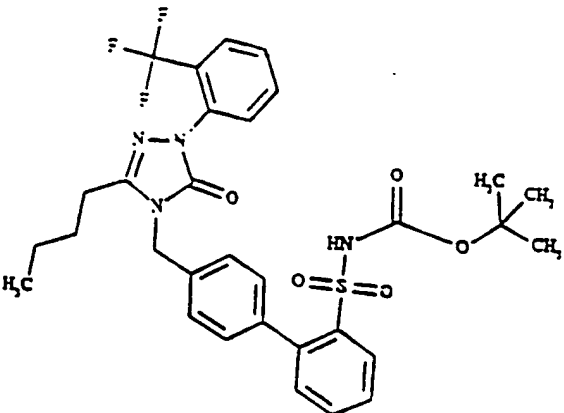
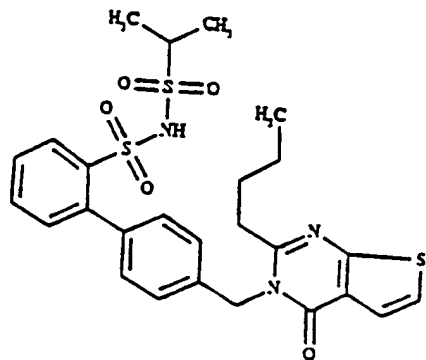
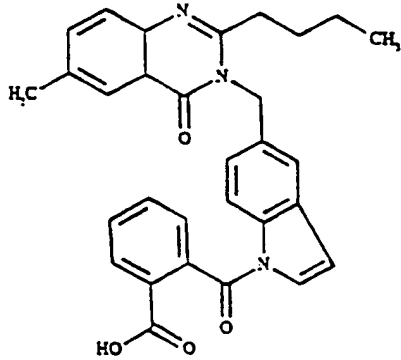
| Compound # | Structure | Source |
|------------|--|---------------------------------|
| 361 |  | EP #513,979 pub. 19 Nov 92 |
| 362 |  | WO #92/20,660 pub. 26 Nov 92 |
| 363 |  | WO #92,20,661 pub. 26 Nov 92 |

TABLE II: Angiotensin II Antagonists

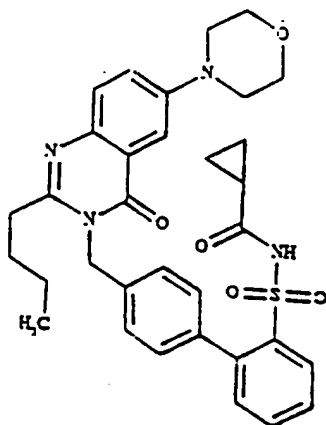
| Compound # | Structure | Source |
|------------|---|---------------------------------|
| 364 |  | WO #92/20,662 pub. 26 Nov 92 |
| 365 |  | WO #92/20,687 pub. 26 Nov 92 |
| 366 |  | EP #517,357 pub. 09 Dec 92 |

147

TABLE II: Angiotensin II Antagonists

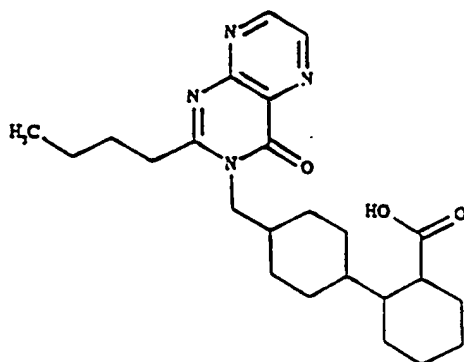
| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

370



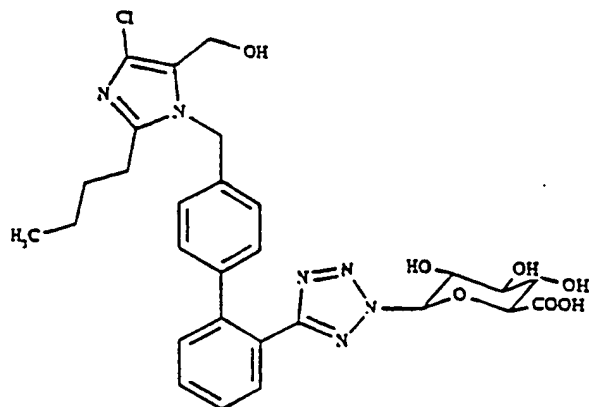
US #5,202,322
pub. 13 Apr 93

371



EP #537,937
pub. 21 Apr 93

372



US #5,217,882
pub. 08 Jun 93

TABLE II: Angiotensin II Antagonists

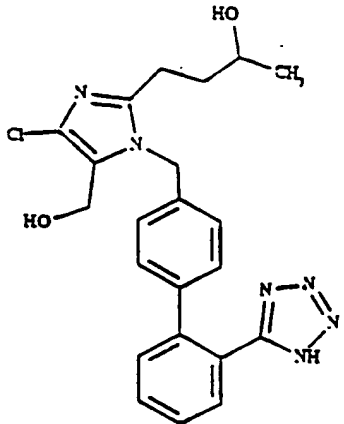
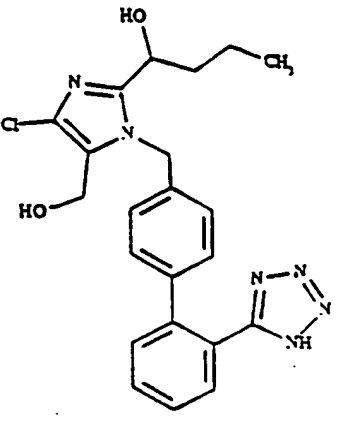
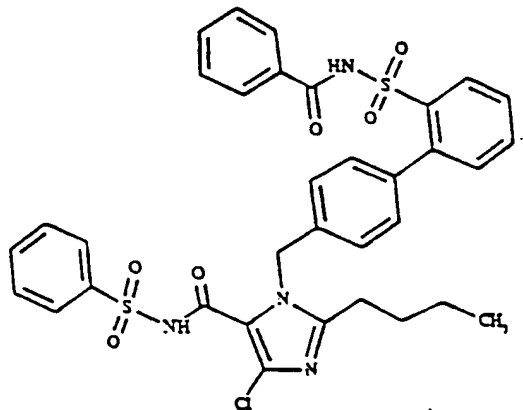
| Compound # | Structure | Source |
|------------|--|---------------------------------|
| 373 |  | US #5,214,153 pub. 25 May 93 |
| 374 |  | US #5,218,125 pub. 08 Jun 93 |
| 375 |  | US #5,236,928 pub. 17 Aug 93 |

TABLE II: Angiotensin II Antagonists

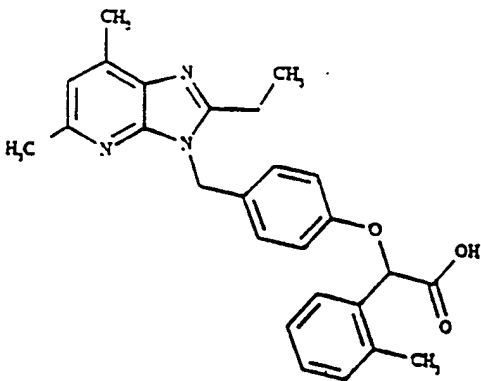
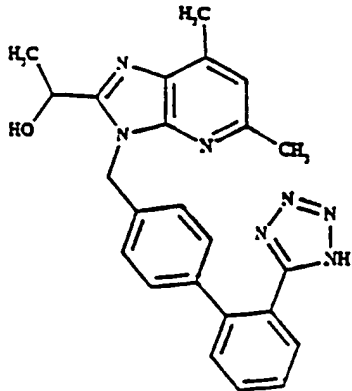
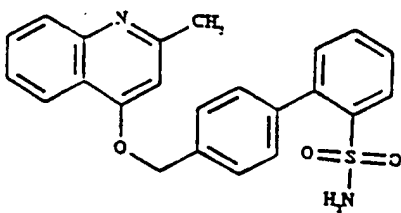
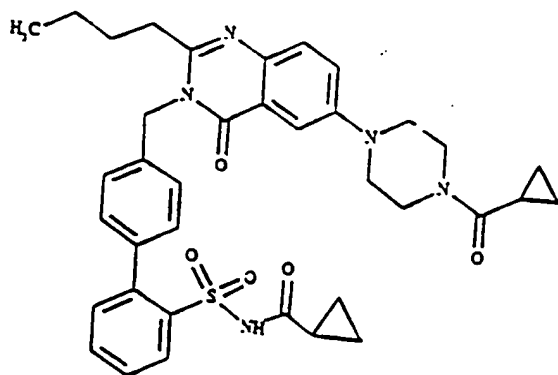
| Compound # | Structure | Source |
|------------|---|---------------------------------|
| 376 |  | US #5,240,938 pub. 31 Aug 93 |
| 377 |  | GB #2,264,709 pub. 08 Sep 93 |
| 378 |  | GB #2,264,710 pub. 08 Sep 93 |

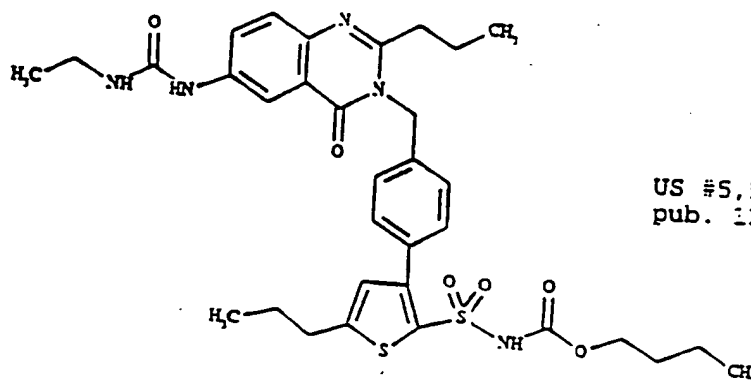
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

379

US #5,256,667
pub. 26 Oct 93

380

US #5,325,574
pub. 12 Oct 93

381

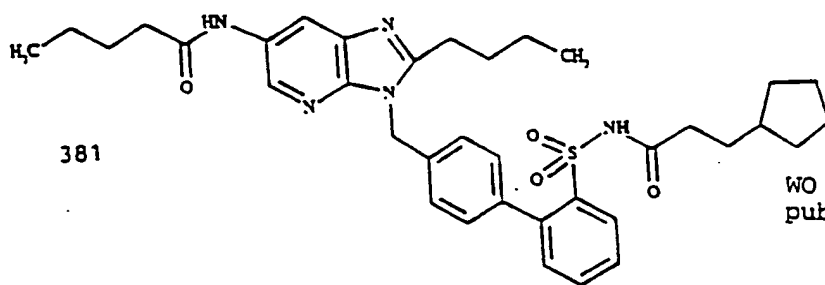
WO #93/23,399
pub. 25 Nov 93

TABLE II: Angiotensin II Antagonists

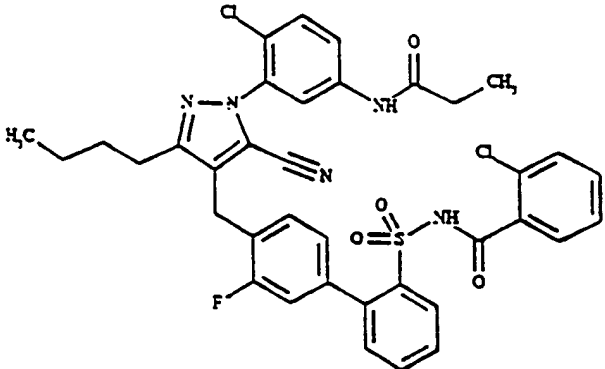
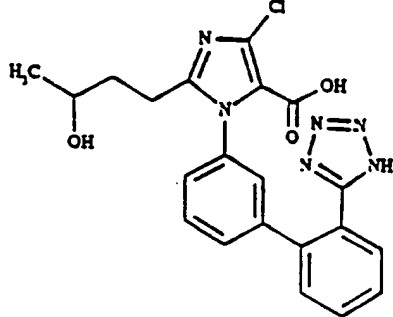
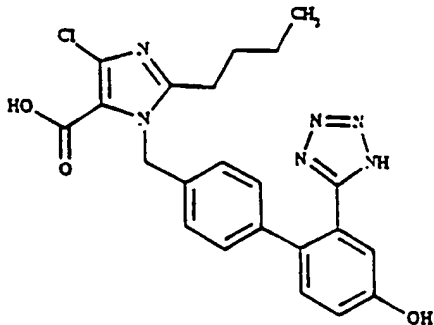
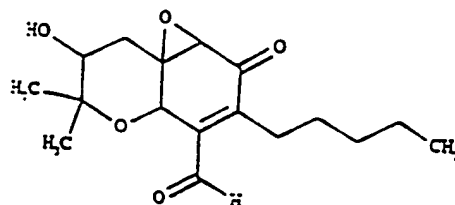
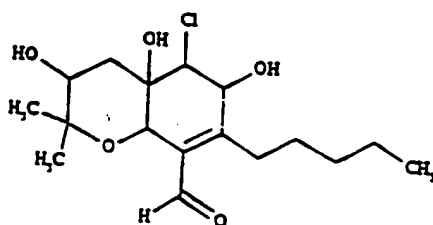
| Compound # | Structure | Source |
|------------|---|---------------------------------|
| 382 |  | US #5,262,412 pub. 16 Nov 93 |
| 383 |  | US #5,264,447 pub. 23 Nov 93 |
| 384 |  | US #5,266,583 pub. 01 Sep 92 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

385

US #5,276,054
pub. 04 Jan 94

386

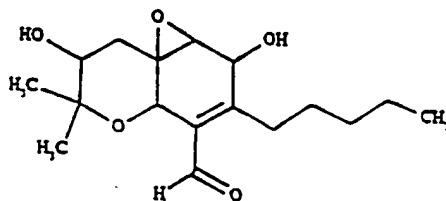
US #5,278,068
pub. 11 Jan 94

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

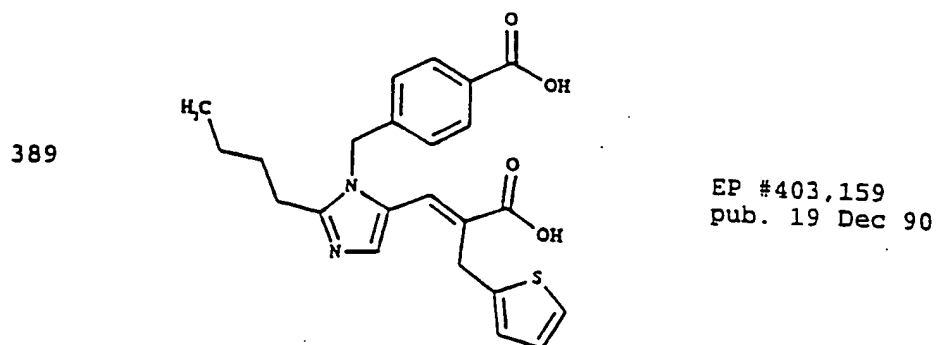
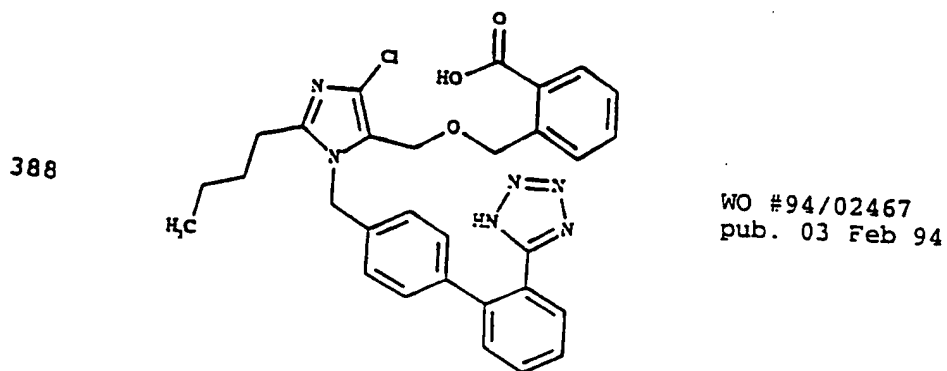
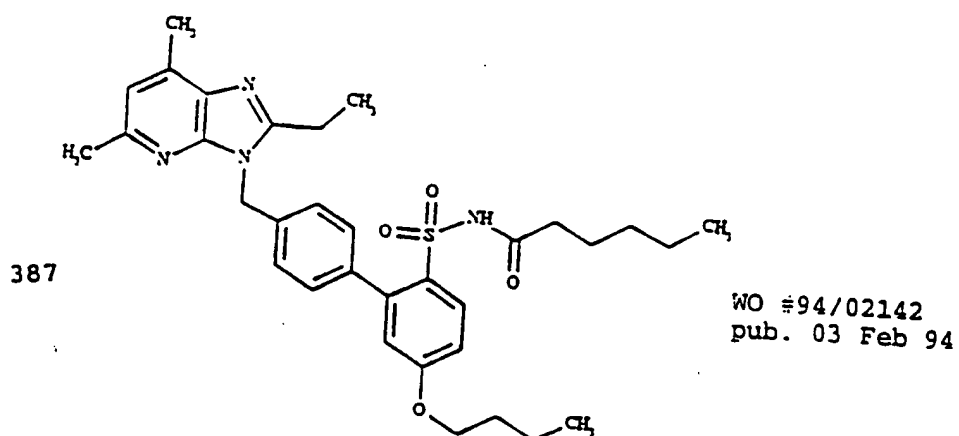


TABLE II: Angiotensin II Antagonists

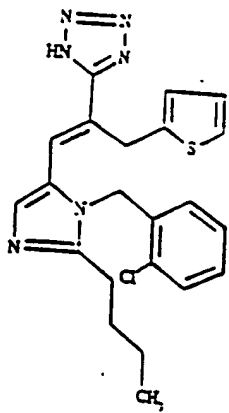
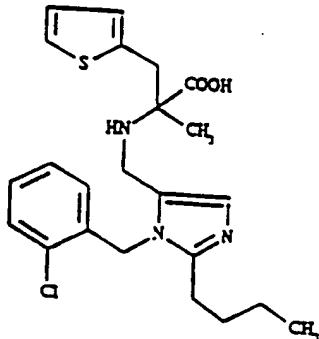
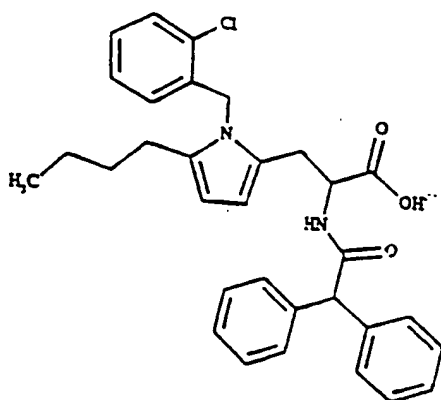
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 390 |  | EP #425,211 pub. 02 May 91 |
| 391 |  | EP #427,463 pub 15 May 91 |
| 392 |  | WO #92/00068 pub. 09 Jan 92 |

TABLE II: Angiotensin II Antagonists

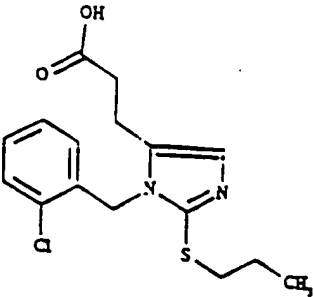
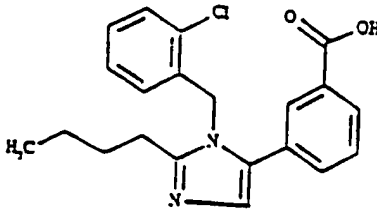
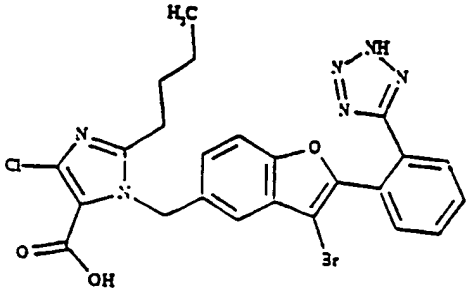
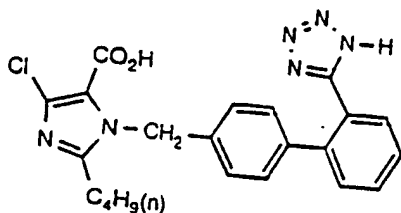
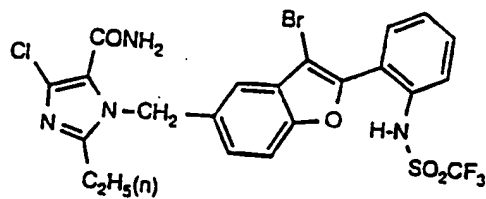
| Compound # | Structure | Source |
|------------|---|---------------------------------|
| 393 |  | WO #92/02,510 pub. 20 Feb 92 |
| 394 |  | WO #92/09278 pub. 11 Jun 92 |
| 395 |  | WO #92/10181 pub. 25 Jun 92 |
| 396 |  | |

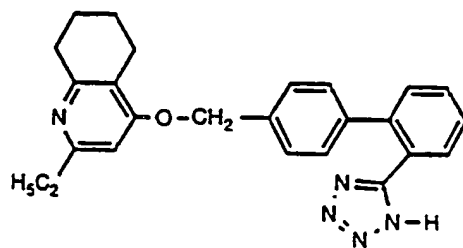
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

397



398



399

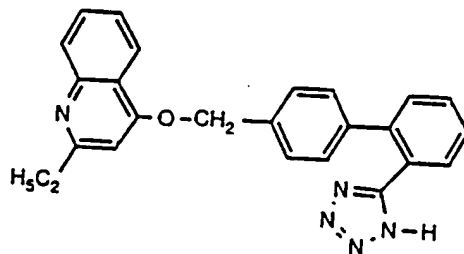
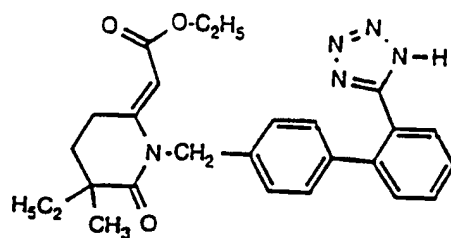


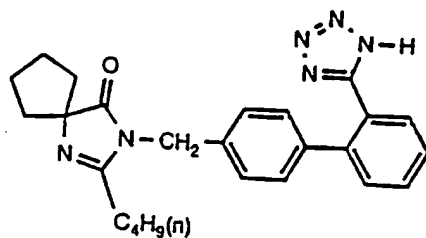
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

400



401



402

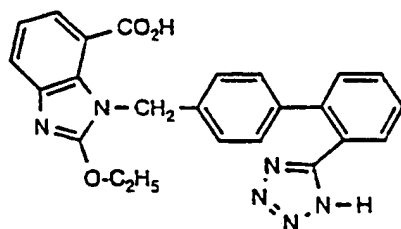
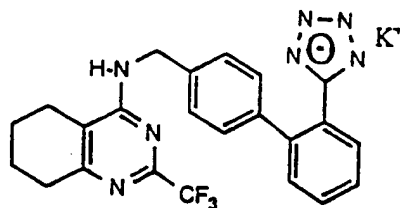


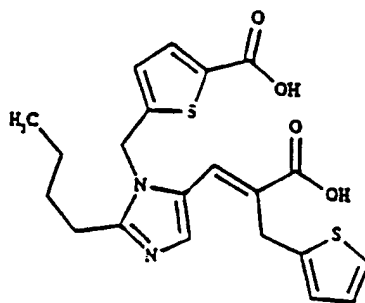
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

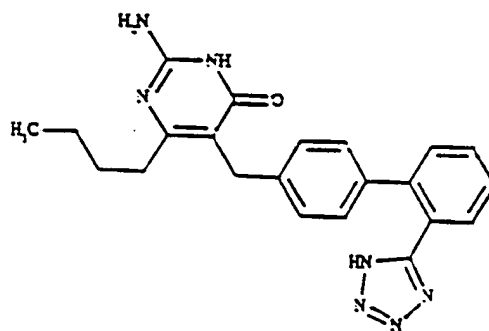
406



407

WO #92/20651
pub. 26 Nov 92

408

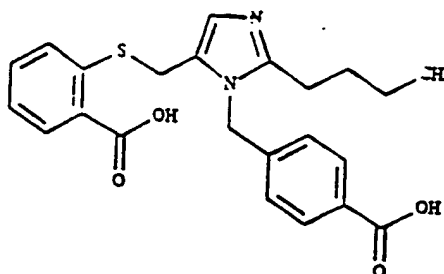
WO #93/03018
pub. 18 Feb 93

160

TABLE II: Angiotensin II Antagonists

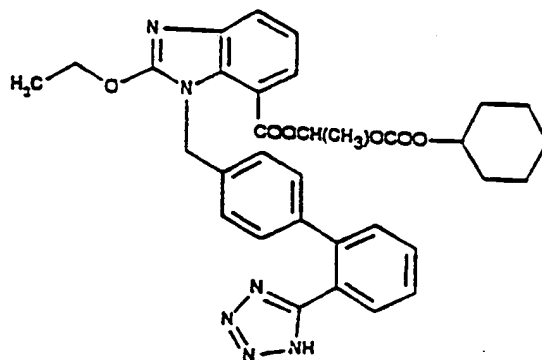
| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

409



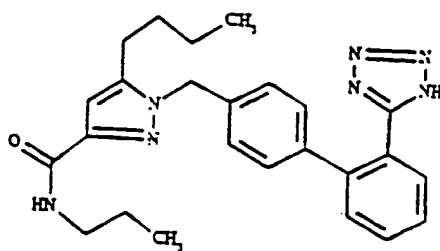
WO #94/00120
pub. 06 Jan 94

410



EP #459,136
pub. 04 Dec 91

411



EP #411,507
pub. 05 Feb 91

TABLE II: Angiotensin II Antagonists

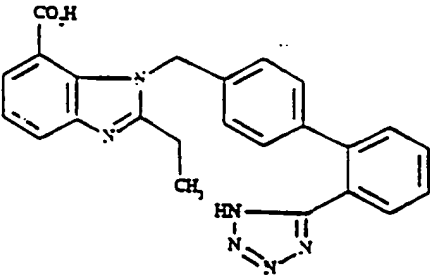
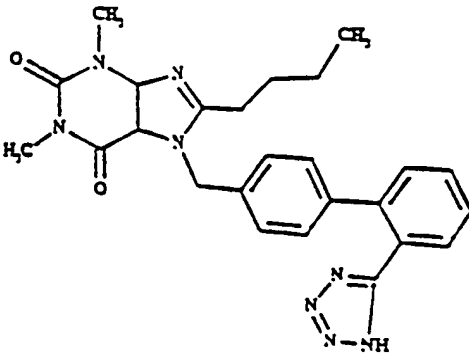
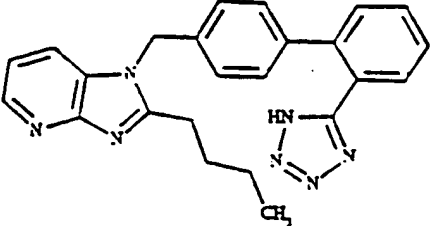
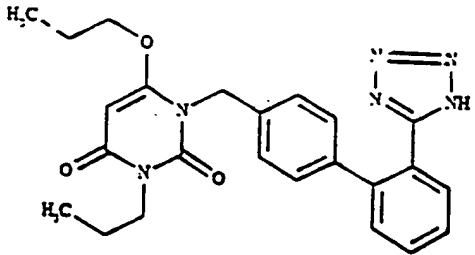
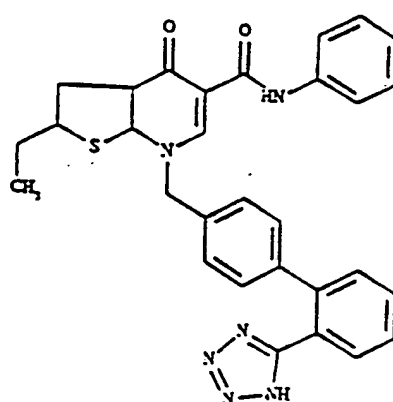
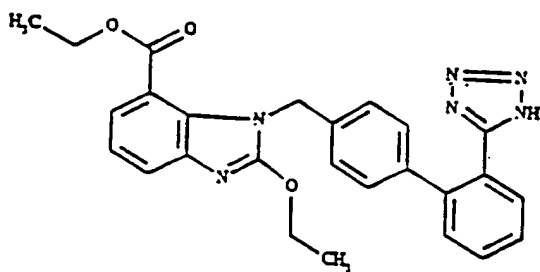
| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 412 |  | EP #425,921 pub. 08 May 91 |
| 413 |  | EP #430,300 pub. 05 Jun 91 |
| 414 |  | EP #434,038 pub. 26 Jun 91 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|--|-------------------------------|
| 415 |  | EP #442,473 pub. 21 Aug 91 |
| 416 |  | EP #443,568 pub. 28 Aug 91 |
| 417 |  | EP #459,136 pub. 04 Dec 91 |

163

TABLE II: Angiotensin II Antagonists

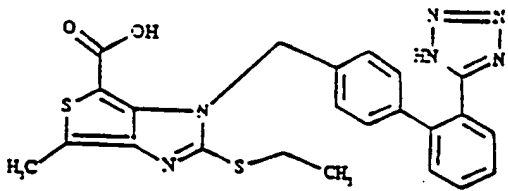
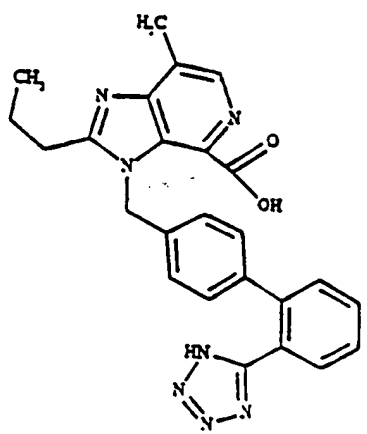
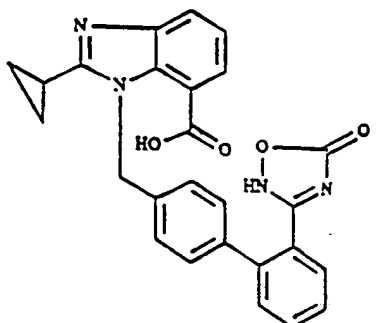
| Compound # | Structure | Source |
|------------|---|-------------------------------|
| 418 |  | EP #483,683 pub. 05 May 92 |
| 419 |  | EP #518,033 pub. 16 Dec 92 |
| 420 |  | EP #520,423 pub. 30 Dec 92 |

TABLE II: Angiotensin II Antagonists

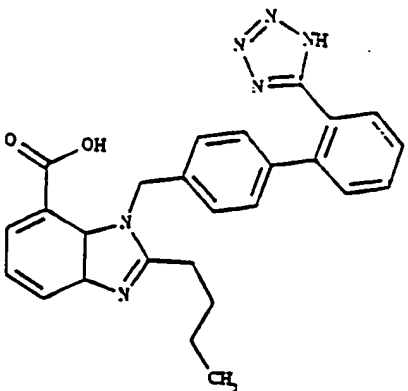
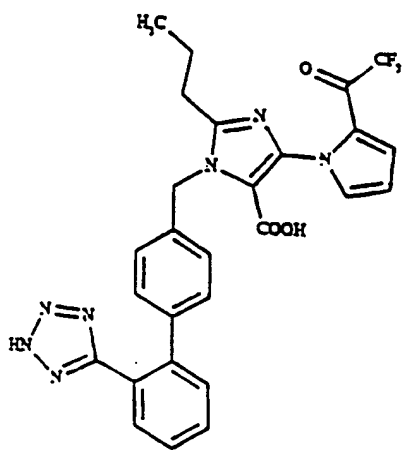
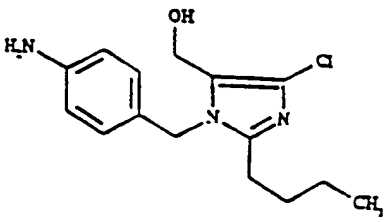
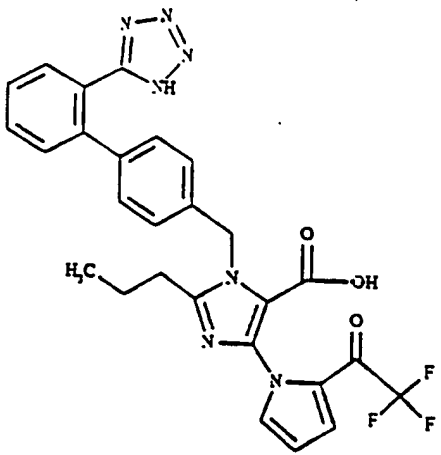
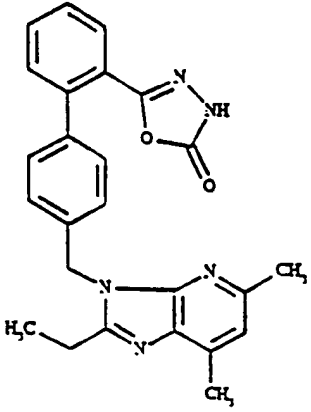
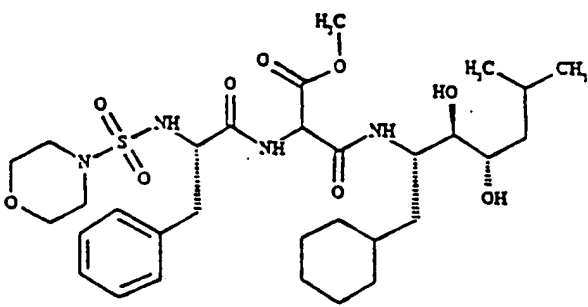
| Compound # | Structure | Source |
|------------|---|--------------------------------|
| 421 |  | EP #546,358 pub. 16 Jun 93 |
| 422 |  | WO #93/00341 pub. 07 Jan 93 |
| 423 |  | WO #92/06081 pub. 16 Apr 92 |

TABLE II: Angiotensin II Antagonists

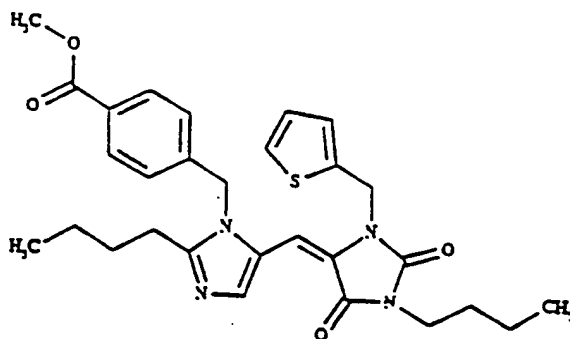
| Compound # | Structure | Source |
|------------|--|---------------------------------|
| 424 |  | WO #93/00341 pub. 07 Jan 93 |
| 425 |  | US #5,210,204 pub. 11 May 93 |
| 426 |  | EP #343,654 pub. 29 Nov 89 |

166

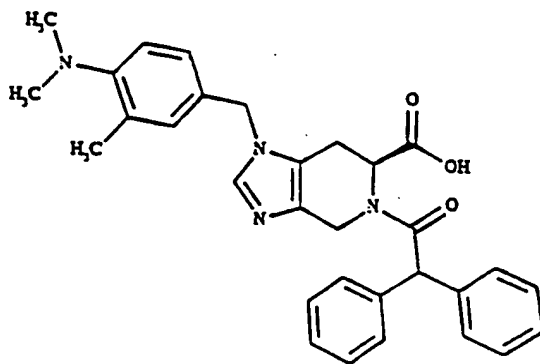
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

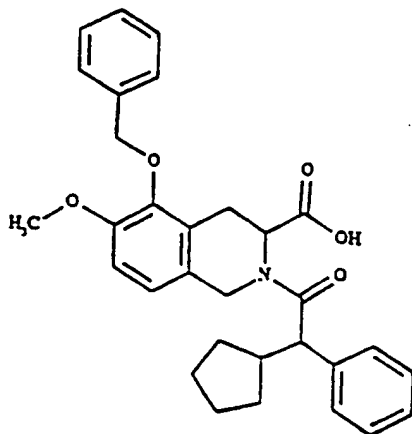
427

WO #93/13077
pub. 08 Jul 93

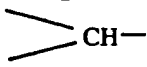
428

WO #93/15734
pub. 19 Aug 93

429

US #5,246,943
pub. 21 Sep 93

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or, as another example, one hydrido group may be attached to a carbon atom

5 to form a  group; or, as another example, two hydrido atoms may be attached to a carbon atom to form a -CH₂- group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched
10 radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The
15 term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is
20 substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a
25 fluoro atom within the group. Dihalalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two
30 chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The term "difluoroalkyl"
35 embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched

alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methylthio group. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenyl-ethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "phenalkyl" and "phenylalkyl" are interchangeable. An example of "phenalkyl" is "phenethyl" which is interchangeable with "phenylethyl". The terms "alkylaryl", "alkoxyaryl" and "haloaryl" denote, respectively, the substitution of one or more "alkyl",

"alkoxy" and "halo" groups, respectively, substituted on an "aryl" nucleus, such as a phenyl moiety. The terms "aryloxy" and "arylthio" denote radicals respectively, provided by aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes, respectively, divalent radicals SO and SO₂. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. "Lower alkanoyl" is an example of a more preferred sub-class of acyl. The term "amido" denotes a radical consisting of nitrogen atom attached to a carbonyl group, which radical may be further substituted in the manner described herein. The term "monoalkylaminocarbonyl" is interchangeable with "N-alkylamido". The term "dialkylaminocarbonyl" is interchangeable with "N,N-dialkylamido". The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted with alkyl groups which may optionally contain additional double-bond unsaturation. The term "heteroaryl", where not otherwise defined before, embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity

of the heteroaryl moiety is preserved after attachment. For any of the foregoing defined radicals, preferred radicals are those containing from one to about ten carbon atoms.

5 Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a
10 plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

 Also included in the combination of the invention
15 are the isomeric forms of the above-described angiotensin II receptor compounds and the epoxy-steroidal aldosterone receptor compounds, including diastereoisomers, regioisomers and the pharmaceutically-acceptable salts thereof. The term
 "pharmaceutically-acceptable salts" embraces salts commonly
20 used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid.
25 Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic
30 acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicylic, phenylacetic, mandelic,
35 embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic,

cyclohexylaminosulfonic, stearic, algenic, β -hydroxybutyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts include metallic salts made from aluminium, calcium, lithium, 5 magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by 10 reacting, for example, the appropriate acid or base with such compound.

BIOLOGICAL EVALUATION

In order to determine the probable effectiveness of a combination therapy for treating or preventing the progression of cardiofibrosis or cardiac hypertrophy, it is important to determine the potency of individual components of the combination therapy. Accordingly, in Assays "A" through "C", the angiotensin II receptor antagonist profiles were determined for many of the compounds described in Table II, herein. In Assay "D", there is described a method for evaluating a combination therapy of the invention, namely, an angiotensin II receptor antagonist of Table II and an epoxy-steroidal aldosterone receptor antagonist of Table I. The efficacy of each of the individual drugs, epoxymexrenone and the angiotensin II receptor blocker, and of these drugs given together at various doses, is evaluated in a rodent model. The methods and results of such assays are described below.

20

Assay A: Angiotensin II Binding Activity

Compounds of the invention were tested for ability to bind to the smooth muscle angiotensin II receptor using a rat uterine membrane preparation. Angiotensin II (AII) was purchased from Peninsula Labs. ^{125}I -angiotensin II (specific activity of 2200 Ci/mmol) was purchased from Du Pont-New England Nuclear. Other chemicals were obtained from Sigma Chemical Co. This assay was carried out according to the method of Douglas et al [Endocrinology, 106, 120-124 (1980)]. Rat uterine membranes were prepared from fresh tissue. All procedures were carried out at 4°C. Uteri were stripped of fat and homogenized in phosphate-buffered saline at pH 7.4 containing 5 mM EDTA. The homogenate was centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM

Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM MgCl₂, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and ¹²⁵I-AII (approximately 10⁵ cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 µM of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC₅₀) of the tested AII antagonist which gives 50% displacement of the total specifically bound ¹²⁵I-AII from the angiotensin II AT₁ receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table III.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

The compounds of the invention were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled

with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (mM): 130 NaCl, 15 NaHCO₃, 15 KCl, 1.2 NaH₂PO₄, 1.2 MgSO₄, 2.5 CaCl₂, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded (3×10^{-10} to 1×10^{-5} M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at 10^{-5} M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA₂ values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The pA₂ value is the concentration of the antagonist which increases the EC₅₀ value for AII by a factor of two. Each test antagonist was evaluated in aorta rings from two rabbits. Results are reported in Table III.

Assay C: In Vivo Intragastric Pressor Assay Response for All Antagonists

25

Male Sprague-Dawley rats weighing 225-300 grams were anesthetized with methohexital (30 mg/kg, i.p.) and catheters were implanted into the femoral artery and vein. The catheters were tunneled subcutaneously to exit dorsally, posterior to the head and between the scapulae. The catheters were filled with heparin (1000 units/ml of saline). The rats were returned to their cage and allowed regular rat chow and water ad libitum. After full recovery from surgery (3-4 days), rats were placed in Lucite holders and the arterial line was connected to a pressure transducer. Arterial pressure was recorded on a Gould polygraph (mmHg). Angiotensin II was administered as a 30

ng/kg bolus via the venous catheter delivered in a 50 μ l volume with a 0.2 ml saline flush. The pressor response in mm Hg was measured by the difference from pre-injection arterial pressure to the maximum pressure achieved. The AII injection was repeated every 10 minutes until three consecutive injections yielded responses within 4 mmHg of each other. These three responses were then averaged and represented the control response to AII. The test compound was suspended in 0.5% methylcellulose in water and was administered by gavage. The volume administered was 2 ml/kg body weight. The standard dose was 3 mg/kg. Angiotensin II bolus injections were given at 30, 45, 60, 75, 120, 150, and 180 minutes after gavage. The pressor response to AII was measured at each time point. The rats were then returned to their cage for future testing. A minimum of 3 days was allowed between tests. Percent inhibition was calculated for each time point following gavage by the following formula: $[(\text{Control Response} - \text{Response at time point}) / \text{Control Response}] \times 100$. Results are shown in Table III.

Assay "D": Renal Hypertensive Rat Model

A combination therapy of an angiotensin II receptor antagonist and an epoxy-steroidal aldosterone receptor antagonist may be evaluated for blood pressure lowering activity in the renal-artery ligated hypertensive rat, a model of high renin hypertension. In this model, six days after ligation of the left renal artery, both plasma renin activity and blood pressure are elevated significantly [J.L. Cangiano et al, J. Pharmacol. Exp. Ther., 206, 310-313 (1979)]. Male Sprague-Dawley rats are instrumented with a radiotelemetry blood pressure transmitter for continuous monitoring of blood pressure. The rats are anesthetized with a mixture of ketamine-HCl (100 mg/kg) and acepromazine maleate (2.2 mg/kg). The abdominal aorta is exposed via a midline incision. Microvascular clamps are placed on the

aorta distal to the renal arteries and at the iliac bifurcation. The aorta is punctured with a 22-gauge needle and the tip of a catheter is introduced. The catheter, which is held in place by a ligature in the psoas muscle, is connected to a radiotelemetry blood pressure transmitter (Mini-Mitter Co., Inc., Sunriver, OR). The transmitter is placed in the peritoneal cavity and sutured to abdominal muscle upon closing of the incision. Rats are housed singly above a radiotelemetry receiver and are allowed standard rat chow and water *ad libitum*. At least 5 days are allowed for recovery from surgery. Mean arterial pressure and heart rate are measured on a Compaq DeskPro 286 AT computer. Data are sampled for 10 seconds at 200-500 hz at 2.5 to 10 min intervals 24 hours per day. After collecting control data for 24 hours, the rats are anesthetized with methohexital (30 mg/kg, i.p.) and supplemented as needed. A midline abdominal incision is made, approximately 2cm in length to expose the left kidney. The renal artery is separated from the vein near the aorta, with care taken not to traumatize the vein. The artery is completely ligated with sterile 4-0 silk. The incision is closed by careful suturing of the muscle layer and skin. Six days later, when MAP is typically elevated by 50-70 mmHg, an AII receptor antagonist, or an aldosterone receptor antagonist, or a combination of the two compounds are administered by gavage each day for about 8 weeks. Single drug dosing is carried out using 20 and 200 mg/kg/day of epoxymexrenone and 1,3,10,30 and 100 mg/kg/day of an AII receptor antagonist. Drug mixtures are obtained by administering a combination of a dose of 1,3,10,30 or 100 mg/kg/day of the AII receptor antagonist with a dose of either 20 or 200 mg/kg/day of the aldosterone antagonist. Blood pressure lowering is monitored by the radiotelemetry system and responses with the compounds are compared to responses obtained in vehicle-treated animals. Plasma and urinary sodium and potassium levels are monitored as a measure of the effectiveness of the aldosterone blockade. Urine samples are collected

overnight using metabolic cages to isolate the samples. Plasma samples are obtained by venous catheterization. Sodium and potassium are measured by flame photometry. Cardiac fibrosis is determined by histological and chemical measurements of the excised hearts following perfusion fixation. Left and right ventricles are weighed, embedded and sectioned. Subsequently, sections are stained with picosirius red and the red staining collagen areas are quantitated by computerized image analysis. The apex of the heart is acid digested and the free hydroxyproline measured colorimetrically. It is expected that MAP will be significantly lowered toward normal pressures in the test animals, treated with the combination therapy and that the condition of myocardial fibrosis will be arrested or avoided.

TABLE III

In Vivo and In Vitro Angiotensin II
Activity of Compounds of the Invention

| 5 | Test | ¹ Assay A | ² Assay B | ³ Assay C | | |
|----|-----------|----------------------|----------------------|----------------------|------------|----------|
| | Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| | Example # | (nM) | | (mg/kg) | (%) | (min.) |
| 10 | 1 | NT | NT | NT | NT | NT |
| | 2 | 95 | 7.37/7.59 | 10 | 95 | 60 |
| | | | | 30 | 98 | 90-120 |
| | 3 | 5.4 | 8.70 ± 0.2 | 10 | 50 | >180 |
| 15 | | | | 30 | 100 | 200+ |
| | 4 | NT | NT | NT | NT | NT |
| | 5 | 200 | 7.48/6.91 | 30 | 38 | 20-30 |
| | 6 | 1300 | 6.55/6.82 | 100 | 90 | 120 |
| 20 | 7 | 84 | 8.01/8.05 | 30 | 90 | 130 |
| | 8 | 17,000 | NT | NT | NT | NT |
| | 9 | 700 | 6.67/6.12 | 30 | 80 | 75 |
| | | | | 100 | 100 | 130 |
| 25 | 10 | 4.9 | 8.19/7.59 | 3 | 86 | 100 |
| | | | | 30 | 100 | 240 |
| | 11 | 160 | 6.45/6.77 | NT | NT | NT |
| | 12 | 6.0 | 8.66/8.59 | NT | NT | NT |
| 30 | 13 | 17 | 8.70/8.85 | NT | NT | NT |
| | 14 | 7.2 | 8.84/8.71 | NT | NT | NT |
| | 15 | 16 | 8.31/8.30 | NT | NT | NT |
| | 16 | 6.4 | 8.95/9.24 | NT | NT | NT |
| 30 | 17 | 4.0 | 8.64/8.40 | NT | NT | NT |
| | 18 | 970 | 6.14/6.09 | NT | NT | NT |
| | 19 | 12,000 | 5.18/5.35 | NT | NT | NT |

| Test | Compound | ¹ Assay A | ² Assay B | ³ Assay C | | |
|-----------|----------|----------------------|----------------------|----------------------|------------|----------|
| | | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| Example # | | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | 20 | 78,000 | 5.89/5.99 | 100 | 10 | 45 |
| | 21 | 87 | 7.71/7.21 | NT | NT | NT |
| | 22 | 460 | 6.60/6.46 | NT | NT | NT |
| | 23 | 430 | 6.48/7.15 | NT | NT | NT |
| | 24 | 10 | 7.56/7.73 | NT | NT | NT |
| 10 | 25 | 480 | 6.80/6.73 | NT | NT | NT |
| | 26 | 3.2 | 9.83/9.66 | 10 | 50 | >180 |
| | 27 | 180 | NT | NT | NT | NT |
| | 28 | 570 | 5.57/6.00 | NT | NT | NT |
| | 29 | 160 | NT | NT | NT | NT |
| 15 | 30 | 22 | 7.73/7.88 | 30 | 50 | >180 |
| | 31 | 14 | NT | NT | NT | NT |
| | 32 | 16 | 7.68/7.29 | NT | NT | NT |
| | 33 | 630 | 6.73/6.36 | NT | NT | NT |
| | 34 | 640 | 5.34/5.69 | NT | NT | NT |
| 20 | 35 | 41 | 7.25/7.47 | NT | NT | NT |
| | 36 | 1400 | 5.92/5.68 | NT | NT | NT |
| | 37 | 340 | 6.90/6.85 | NT | NT | NT |
| | 38 | 10 | 7.82/8.36 | NT | NT | NT |
| | 39 | 10 | 7.88/7.84 | NT | NT | NT |
| 25 | 40 | 83 | 7.94/7.61 | NT | NT | NT |
| | 41 | 3700 | 5.68/5.96 | NT | NT | NT |
| | 42 | 370 | 6.56/6.26 | NT | NT | NT |
| | 43 | 19 | 8.97/8.61 | NT | NT | NT |
| | 44 | 16 | 8.23/7.70 | NT | NT | NT |
| 30 | 45 | 4.4 | 8.41/8.24 | NT | NT | NT |
| | 46 | 110 | 6.80/6.64 | NT | NT | NT |

| Test | Compound | ¹ Assay A | ² Assay B | ³ Assay C | | |
|-----------|----------|----------------------|----------------------|----------------------|------------|----------|
| | | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| Example # | | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | 47 | 21 | 7.85/7.58 | NT | NT | NT |
| | 48 | 680 | 6.27/6.75 | NT | NT | NT |
| | 49 | 120 | 7.06/7.07 | NT | NT | NT |
| | 50 | 54 | 7.71/7.89 | NT | NT | NT |
| | 51 | 8.7 | 8.39/8.51 | NT | NT | NT |
| 10 | 52 | 100 | 8.14/8.12 | NT | NT | NT |
| | 53 | 65 | 7.56/7.83 | NT | NT | NT |
| | 54 | 3100 | 6.02 | NT | NT | NT |
| | 55 | 80 | 6.56/7.13 | NT | NT | NT |
| | 56 | 5.0 | 9.04/8.35 | NT | NT | NT |
| 15 | 57 | 2300 | 6.00 | NT | NT | NT |
| | 58 | 140 | 6.45/6.57 | NT | NT | NT |
| | 59 | 120 | 7.23/7.59 | NT | NT | NT |
| | 60 | 2200 | 6.40/6.03 | NT | NT | NT |
| | 61 | 110 | 7.29/7.70 | NT | NT | NT |
| 20 | 62 | 26 | 8.69/8.61 | NT | NT | NT |
| | 63 | 61 | 7.77/7.67 | NT | NT | NT |
| | 64 | 54 | 7.00/6.77 | NT | NT | NT |
| | 65 | 23 | 7.85/7.75 | NT | NT | NT |
| | 66 | 12 | 9.34/8.58 | NT | NT | NT |
| 25 | 67 | 3100 | 5.88/5.78 | NT | NT | NT |
| | 68 | 8.6 | 8.19/8.65 | NT | NT | NT |
| | 69 | 15 | 7.80/8.28 | NT | NT | NT |
| | 70 | 44 | 7.71/8.05 | NT | NT | NT |
| | 71 | 12,000 | * | NT | NT | NT |
| 30 | 72 | 83 | 6.11/6.10 | NT | NT | NT |
| | 73 | 790 | 7.65/7.46 | NT | NT | NT |

| Test | ¹ Assay A | | ² Assay B | ³ Assay C | | |
|------|----------------------|------------------|----------------------|----------------------|------------|----------|
| | Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| | Example # | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | 74 | 6.5 | 8.56/8.39 | NT | NT | NT |
| | 75 | 570 | 6.00/5.45 | NT | NT | NT |
| | 76 | 5400 | 5.52/5.78 | NT | NT | NT |
| | 77 | 15,000 | 5.77 | NT | NT | NT |
| | 78 | 101 | 7.0 | | 93 | 60-100 |
| 10 | 79 | 4.9 | 9.2 | | 100 | >200 |
| | | | | | 50 | >180 |
| | 80 | 25 | 8.1 | | NT | NT |
| | 81 | 18 | 8.0 | | 40 | 180 |
| | 82 | 7.9 | 8.5 | | 20 | 180 |
| 15 | 83 | 3.6 | 8.3 | | 15 | >180 |
| | 84 | 16 | 7.1 | | 20 | 30 |
| | 85 | 8.7 | 8.9 | | NT | NT |
| | 86 | 9 | 7.8 | | NT | NT |
| | 87 | 91 | 7.8 | | NT | NT |
| 20 | 88 | 50 | 7.7 | | NT | NT |
| | 89 | 18 | 7.9 | | NT | NT |
| | 90 | 5.6 | 9.0 | | NT | NT |
| | 91 | 30 | 8.6 | | 40 | >180 |
| | 92 | 35 | 7.9 | | NT | NT |
| 25 | 93 | 480 | NT | | NT | NT |
| | 94 | 5,800 | NT | | NT | NT |
| | 95 | 66 | 8.2 | | NT | NT |
| | 96 | 21 | 8.0 | | NT | NT |
| | 97 | 280 | 7.7 | | NT | NT |
| 30 | 98 | 22 | 8.1 | | NT | NT |
| | 99 | 280 | 6.5 | | NT | NT |
| | 100 | 4.4 | 9.4 | | NT | NT |
| | 101 | 36 | 7.8 | | NT | NT |

| Test | ¹ Assay A | ² Assay B | ³ Assay C | | |
|-----------|----------------------|----------------------|----------------------|------------|----------|
| Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| Example # | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | 102 | 43 | 7.7 | NT | NT |
| | 103 | 12 | 8.0 | NT | NT |
| | 104 | 15 | 8.0 | NT | NT |
| | 105 | 290 | 6.6 | NT | NT |
| | 106 | 48 | 7.7 | NT | NT |
| 10 | 107 | 180 | 8.3 | NT | NT |
| | 108 | 720 | 5.3 | 100 | 45 |
| | 109 | 250 | 7.3 | 30 | 50 |
| | 110 | 590 | 6.4 | NT | NT |
| | 111 | 45 | 9.0 | 30 | 87 |
| 15 | 112 | 2000 | 5.2 | NT | NT |
| | 113 | 12 | 8.4 | 10 | 60 |
| | 114 | 400 | 6.4 | NT | NT |
| | 115 | 11 | 8.2 | 3 | 40 |
| | 116 | 230 | 6.5 | NT | >240 |
| 20 | 117 | 170 | 6.5 | NT | NT |
| | 118 | 37 | 9.21/9.17 | 10 | 70 |
| | 119 | 16 | 9.21/9.00 | 3 | 20 |
| | 120 | 25 | 9.05/8.77 | 10 | 80 |
| | 121 | 46 | NT | NT | NT |
| 25 | 122 | 46 | NT | NT | NT |
| | 123 | 50 | NT | NT | NT |
| | 124 | 40 | 9.42/9.12 | 3 | 45 |
| | 125 | 40 | 9.25/8.80 | 3 | 35 |

| Test | ¹ Assay A | | ² Assay B | | ³ Assay C | |
|------|----------------------|------------------|----------------------|---------|----------------------|----------|
| | Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| | Example # | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | 126 | 240 | 7.20/7.05 | | NT | |
| | 127 | 12,000 | 4.96 | | NT | |
| | 128 | 16 | 8.63/8.40 | | NT | |
| | 129 | 6,700 | 5.30 | | NT | |
| | 130 | 40 | 8.10/7.94 | | NT | |
| 10 | 131 | 9.5 | 7.53/8.25 | | | |
| | 132 | 12 | 8.6 | | NT | |
| | 133 | 10 | 8.7 | 3 | 20 | 180 |
| | | | | | | 90-120 |
| 15 | 134 | 22 | 9.3 | 3 | 35 | 180 |
| | 135 | 16 | 8.5 | 3 | 35 | >180 |
| | 136 | NT | NT | | NT | |
| | 137 | 220 | 8.3 | | NT | |
| | 138 | 130 | 8.2 | | NT | |
| 20 | 139 | 0.270 | 6.3 | | NT | |
| | 140 | 0.031 | 8.1 | | 100 | 160 |
| | 141 | 0.110 | 8.02 | | NT | NT |
| | 142 | 2.000 | NA | | NT | NT |
| | 143 | 0.052 | 7.7 | | 85 | 75 |
| 25 | 144 | 0.088 | 7.7 | | 50 | 125 |
| | 145 | 0.480 | 6.7 | | NT | NT |
| | 146 | 0.072 | 6.4 | | NT | NT |

| Test | ¹ Assay A | ² Assay B | ³ Assay C | | | |
|-----------|----------------------|----------------------|----------------------|------------|----------|-------|
| Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration | |
| Example # | (nM) | | (mg/kg) | (%) | (min.) | |
| 5 | 147 | 5.8 | 5.6 | 3 | 74 | 5-10 |
| | 148 | 0.87 | 5.8 | 3 | 92 | 20-30 |
| | 149 | 1.1 | 6.1 | 3 | NT | NT |
| | 150 | 14 | 8.03/7.80 | 3 | 25 | >180 |
| | 151 | 17 | 7.76/7.97 | 3 | 15 | 180 |
| 10 | 152 | 150 | 7.46/7.23 | 3 | 10 | 140 |
| | 153 | 13 | 8.30/7.69 | 3 | 25 | >180 |
| | 154 | 97 | 8.19/8.38 | | NA | |
| | 155 | 86 | 7.60/7.14 | | NA | |
| | 156 | 78 | 8.03/7.66 | | NA | |
| 15 | 157 | 530 | /6.22 | | NA | |
| | 158 | 54 | 8.23/8.14 | 3 | 30 | >180 |
| | 159 | 21 | 7.92/7.56 | 3 | 10 | 150 |
| | 160 | 64 | 7.87/7.71 | | | |
| | 161 | 28 | | | NA | |
| 20 | 162 | 380 | 6.21/6.55 | | NA | |
| | 163 | 420 | 7.42/6.75 | | NA | |
| | 164 | 1700 | | | NA | |
| | 165 | 410 | 6.90/7.18 | | NA | |

| Test Compound | Example # | ¹ Assay A | ² Assay B | ³ Assay C | | |
|------------------|-----------|----------------------|----------------------|----------------------|------------|----------|
| | | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| | | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | 166 | 160 | 7.57/7.74 | | NA | |
| | 167 | 370 | 7.08/7.11 | | NA | |
| | 168 | 420 | 7.69/7.58 | | NA | |
| | 169 | 150 | 7.78/7.58 | 3 | 15 | 180 |
| | 170 | 26 | 7.08/7.77 | 3 | 40 | >180 |
| 10 | 171 | 28 | 7.52/7.11 | 3 | 0 | 0 |
| | 172 | 70 | 7.15/7.04 | | NA | |
| | 173 | 90 | 7.49/6.92 | | NA | |
| | 174 | 180 | 7.29/7.02 | | NA | |
| | 175 | 27 | NA | 3 | 0 | 0 |
| 15 | 176 | 9.8 | 7.69/7.55 | 3 | 10 | 150 |
| | 177 | 26 | 7.41/7.85 | 3 | 15 | 180 |
| | 178 | 88 | 7.54/7.47 | | NA | |
| | 179 | 310 | 6.67/ - | | NA | |
| | 180 | 20 | 7.56/7.15 | 3 | 25 | 180 |
| 20 | 181 | 21 | 7.70/7.12 | 3 | 20 | 180 |
| | 182 | 59 | NA | | NA | |
| | 183 | 390 | NA | | NA | |
| | 184 | 1100 | 6.78/ - | | NA | |

| Test | ¹ Assay A | ² Assay B | ³ Assay C | | | |
|-----------|----------------------|----------------------|----------------------|------------|----------|-------|
| Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration | |
| Example # | (nM) | | (mg/kg) | (%) | (min.) | |
| 5 | 185 | 6.5 | 8.82/8.53 | 3 | 50 | > 180 |
| | 186 | 38 | 8.13/7.40 | 3 | 25 | 180 |
| | 187 | 770 | 7.46/6.95 | | NA | |
| | 188 | 140 | 7.72/7.09 | | NA | |
| | 189 | 29 | 8.64/8.23 | | NA | |
| 10 | 190 | 10 | 7.87/7.89 | 3 | 10 | 180 |
| | 191 | 81 | 7.75/7.76 | 3 | 10 | 180 |
| | 192 | 140 | | | NA | |
| | 193 | 11 | 9.27/8.87 | 3 | 10 | 180 |
| | 194 | 47 | 7.64/7.35 | | NA | |
| 15 | 195 | 34 | 8.44/8.03 | | NA | |
| | 196 | 31 | 7.68/8.26 | | NA | |
| | 197 | 14 | 8.03/8.60 | | NA | |
| | 198 | 7.6 | 8.76/8.64 | 3 | 35 | > 180 |
| | 199 | 10 | 8.79/8.85 | 3 | 60 | > 180 |
| 20 | 200 | 20 | 8.42/8.77 | 3 | 45 | > 180 |
| | 201 | 17 | 8.78/8.63 | 3 | 10 | 180 |
| | 202 | 12 | 8.79/8.64 | 3 | 65 | > 180 |
| | 203 | 9.2 | 8.43/8.36 | 3 | 50 | > 180 |
| | 204 | 16 | 9.17/8.86 | 3 | 75 | > 180 |
| 25 | 205 | 20 | 9.14/9.15 | 3 | 40 | > 180 |
| | 206 | 5.4 | 8.75/8.89 | 3 | 30 | > 180 |
| | 207 | 99 | 9.04/8.60 | | NA | |
| | 208 | 22 | 9.19/8.69 | 3 | 50 | > 180 |
| | 209 | 5.0 | 9.41/9.16 | 3 | 25 | > 180 |
| 30 | 210 | 3.6 | 8.36/8.44 | 3 | 15 | 180 |
| | 211 | 18 | 8.74/8.67 | 3 | 35 | > 180 |
| | 212 | 23 | 8.85/8.25 | 3 | 15 | 180 |
| | 213 | 51 | NA | | NA | |
| | 214 | 65 | NA | | NA | |
| 35 | 215 | 45 | NA | | NA | |
| | 216 | 5.4 | 8.80/9.04 | 3 | 50 | > 180 |

| Test | ¹ Assay A | ² Assay B | ³ Assay C | | |
|-----------|----------------------|----------------------|----------------------|------------|----------|
| Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| Example # | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | | | | | |
| 217 | 9.4 | NA | 3 | 65 | > 180 |
| 218 | 9.0 | NA | | NA | |
| 219 | 14 | NA | | NA | |
| 220 | 7.0 | NA | 3 | 75 | 120 |
| 10 | | | | | |
| 221 | 4.8 | NA | 3 | 25 | > 180 |
| 222 | 5.0 | NA | | NA | |
| 223 | 14 | 7.45/7.87 | 3 | 20 | > 180 |
| 224 | 91 | NA | | NA | |
| 225 | 160 | NA | | NA | |
| 15 | | | | | |
| 226 | 93 | NA | | NA | |
| 227 | 89 | 7.55/7.67 | | NA | |
| 228 | 4.5 | 9.17/8.25 | 3 | 80 | >180 |
| 229 | 19 | NT | 3 | 40 | >180 |
| 230 | 2.6 | 8.23/8.69 | 3 | 25 | >180 |
| 20 | | | | | |
| 231 | 3.6 | NT | 3 | 75 | >180 |
| 232 | 4.4 | 8.59/8.89 | 3 | 70 | >180 |
| 233 | 84 | 8.51/8.78 | | NT | |
| 234 | 5.0 | 8.49/9.00 | 3 | 20 | - |
| 235 | 34 | 7.14/7.07 | | NT | |
| 25 | | | | | |
| 236 | 4.9 | NC | 3 | 70 | >180 |
| 237 | 3.6 | NT | | NT | |
| 238 | 1.7 | NT | 3 | 15 | >180 |
| 239 | 6.8 | 7.88/8.01 | 3 | 20 | >180 |
| 240 | 120 | NA | | NA | |
| 30 | | | | | |
| 241 | 6.9 | 8.57/8.24 | 3 | 40 | >180 |
| 242 | 110 | 7.11/6.60 | | NA | |
| 243 | 250 | NA | | NA | |
| 244 | 150 | 7.17/7.17 | | NA | |
| 245 | 98 | 6.64/7.04 | | NA | |
| 35 | | | | | |
| 246 | 72 | 7.46/7.59 | | NA | |
| 247 | 9.4 | 8.26/8.41 | 3 | 20 | 180 |

| Test | ¹ Assay A | ² Assay B | ³ Assay C | | |
|-----------|----------------------|----------------------|----------------------|------------|----------|
| Compound | IC ₅₀ | pA ₂ | Dose | Inhibition | Duration |
| Example # | (nM) | | (mg/kg) | (%) | (min.) |
| 5 | 248 | 20 | 7.68/7.50 | 3 | 10 |
| | 249 | 4.4 | NA | 3 | 20 |
| | 250 | 43 | NA | 3 | 0 |
| | 251 | 25 | NA | | NA |
| | 252 | 13 | NA | | NA |
| 10 | 253 | 2.6 | NA | | NA |
| | 254 | 72 | NA | | NA |
| | 255 | 12 | 7.61/7.46 | 3 | 20 |
| | 256 | 4.1 | 8.43/7.78 | 3 | 30 |
| | 257 | 160 | 6.63/6.68 | | NA |
| 15 | 258 | 350 | 6.84/6.84 | | NA |
| | 259 | 54 | NA | | NA |
| | 260 | 220 | NA | | NA |
| | 261 | 18 | NA | | NA |
| | 262 | 530 | -/6.22 | | NA |
| 20 | 263 | 57 | NA | | NA |
| | 264 | 11 | NA | | NA |
| | 265 | 110 | NA | | NA |
| | 266 | 290 | NA | | NA |
| | 267 | 25 | NA | 3 | 25 |
| 25 | 268 | 520 | NA | 3 | 0 |
| | 269 | 9.7 | NA | | NA |
| | 270 | 21 | NA | | NA |
| | 271 | 14 | NC | 3 | 20% |
| | 272 | 97 | NC | 3 | 70% |
| 30 | 273 | 9.8 | 8.53/8.61 | 3 | 25% |
| | 274 | 13 | 9.06/8.85 | 3 | 35% |
| | 275 | 6.3 | 9.07/ -- | 3 | 40% |
| | 276 | 33 | 8.71/8.64 | 3 | <20% |
| | 277 | 190 | -- /6.54 | | NT |
| 35 | 278 | 30 | 8.49/8.51 | 3 | 50% |
| | 279 | 270 | 8.06/8.25 | | NT |
| | 280 | 480 | 6.41/6.35 | NT | NT |

NT = NOT TESTED

NC = Non-Competitive antagonist

5 *Antagonist Activity not observed up to 10 μ M of test
compound.

1Assay A: Angiotensin II Binding Activity

2Assay B: In Vitro Vascular Smooth Muscle Response

3Assay C: In Vivo Pressor Response

10

Test Compounds administered intragastrically, except for
compounds of examples #1-#2, #4-#25, #27-#29, #30-#79,
#108-#109, #111, #118 and #139-#149 which were given
intraduodenally.

15

Administration of the angiotensin II receptor antagonist and the aldosterone receptor antagonist may take place sequentially in separate formulations, or may be
5 accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous
10 isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropyl-methyl cellulose, together with one or more
15 of a lubricant, preservative, surface-active or dispersing agent.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet,
20 capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of each active
25 ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.01 to 30 mg/kg body weight, particularly from about 1 to 15 mg/kg body weight,
30 may be appropriate.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A
35 suitable daily dose of each active component is from about 0.01 to 15 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred

daily dose would be from about 1 to 10 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 15 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 15 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 10 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

In combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 5 mg to about 400 mg, and the AII antagonist may be present in an amount in a range from about 1 mg to about 800 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 400:1 to about 1:160.

In a preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 10 mg to about 200 mg, and the AII antagonist may be present in an amount in a range from about 5 mg to about 600 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 40:1 to about 1:60.

In a more preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 20 mg to about 100 mg, and the AII antagonist may be present in an amount in a range from about 10 mg to about 400 mg, which represents aldosterone

antagonist-to-AII antagonist ratios ranging from about 10:1 to about 1:20.

The dosage regimen for treating a disease condition with the combination therapy of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the active components of this combination therapy invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the components may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The components may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What Is Claimed Is:

1. A method to treat a subject susceptible to or afflicted with cardiofibrosis or cardiac hypertrophy, which method comprises administering a combination of drug agents comprising a therapeutically-effective amount of an angiotensin II receptor antagonist and a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist.
2. The method of Claim 1 wherein said epoxy-steroidal aldosterone receptor antagonist is selected from epoxy-containing compounds.
3. The method of Claim 2 wherein said epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroidal nucleus of a 20-spiroxane compound.
4. The method of Claim 3 wherein said 20-spiroxane compound is characterized by the presence of a 9 α -, 11 α -substituted epoxy moiety.
5. The method of Claim 2 wherein said epoxy-containing compound is selected from the group consisting of
- pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ -lactone, methyl ester, (7 α ,11 α ,17 α)-;
- pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 α ,11 α ,17 α)-;
- 3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -lactone, (6 β ,7 β ,11 β ,17 β)-;
- pregn-4-ene-7,21-dicarboxylic acid,9,11-

epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester,
monopotassium salt, (7 α ,11 α ,17 α)-;

5 pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-
17-hydroxy-3-oxo-,7-methyl ester, monopotassium
salt, (7 α ,11 α ,17 α)-;

3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-
carboxylic acid, 9,11-epoxy-6,7-dihydro-17-
10 hydroxy-3-oxo-, γ -lactone(6 α ,7 α ,11 α)-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,
methyl ester, (6 α ,7 α ,11 α ,17 α)-;

15
3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,
monopotassium salt, (6 α ,7 α ,11 α ,17 α)-;

20 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -
lactone, (6 α ,7 α ,11 α ,17 α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
25 17-hydroxy-3-oxo-, γ -lactone, ethyl ester,
(7 α ,11 α ,17 α)-; and

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-
17-hydroxy-3-oxo-, γ -lactone, 1-methylethyl
30 ester, (7 α ,11 α ,17 α)-.

6. The method of Claim 1 wherein said
angiotensin II receptor antagonist is selected from
compounds consisting of a first portion and a second
35 portion, wherein said first portion is selected from a
fragment of Formula I:

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Ar-Alk-L

Ar-L-Ar-Alk-L

Het-L-Ar-Alk-L

Het-L-Het-Alk-L

(I)

5

Ar-L-Het-Alk-L

Het-L-Alk-L

wherein Ar is a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being fully unsaturated or partially or fully saturated;

wherein Het is a monocyclic or bicyclic fused ring system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from one or more hetero atoms selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members;

20

wherein Alk is an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms;

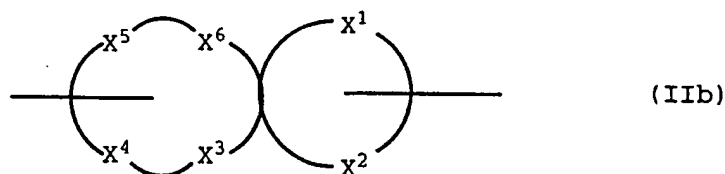
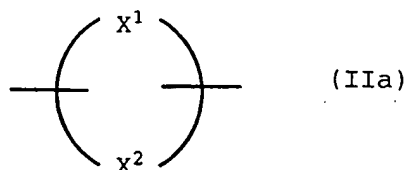
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wherein L is a straight bond or a bivalent linker moiety selected from carbon, oxygen and sulfur;

and wherein said second portion is a monocyclic heterocyclic moiety selected from moieties of Formula IIa or is a bicyclic heterocyclic moiety selected from moieties of Formula IIb:

30

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wherein each of X¹ through X⁶ is selected from -CH=, -CH₂-, -N=, -NH-, O, and S, with the proviso that at least one of X¹ through X⁶ in each of Formula IIa and Formula IIb must be a hetero atom, and wherein said heterocyclic moiety of Formula IIa or IIb may be attached through a bond from any ring member of the Formula IIa or IIb heterocyclic moiety having a substitutable or a bond-forming position.

7. The method of Claim 6 wherein said monocyclic heterocyclic moiety of Formula IIa is selected from thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl, 1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

8. The method of Claim 7 wherein said bicyclic heterocyclic moiety of Formula IIb is selected from benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiololo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

9. The method of Claim 8 wherein said angiotensin II receptor antagonist compound having said first-and-second-portion moieties of Formula I and II is further characterized by having an acidic moiety attached to either of said first-and-second-portion moieties.

10. The method of Claim 9 wherein said acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:



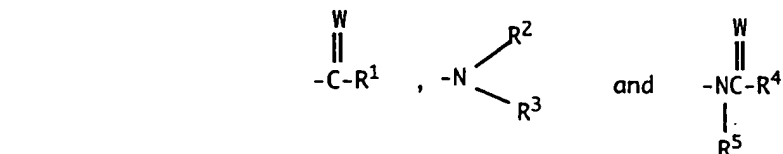
wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties;

wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

11. The method of Claim 10 wherein said acidic moiety is selected from carboxyl moiety and tetrazolyl moiety.

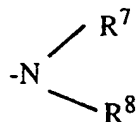
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12. The method of Claim 10 wherein any of the moieties of Formula I and Formula II may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

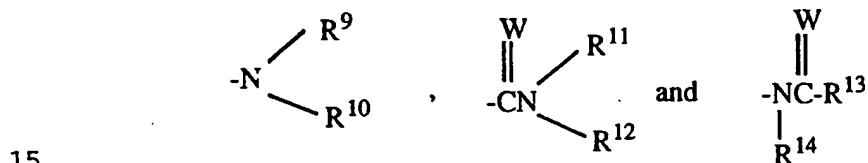


30 wherein W is oxygen atom or sulfur atom; wherein each of R¹ through R⁵ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR⁶ and

200



wherein Y is selected from oxygen atom and sulfur atom and R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R¹, R², R³, R⁴, R⁵, R⁷ and R⁸ is further independently selected from amino and amido radicals of the formula



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wherein W is oxygen atom or sulfur atom; wherein each of R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R² and R³ taken together and each of R⁴ and R⁵ taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of R² and R³ taken together and each of R⁷ and R⁸ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido

30

radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

5

13. The method of Claim 12 wherein said angiotensin II receptor antagonist is 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor antagonist is

10 9 α -, 11 α -epoxy-7 α -methoxycarbonyl-20-spirox-4-ene-3,21-dione or a pharmaceutically-acceptable salt thereof.

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14. The method of Claim 13 further characterized by said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about twenty-to-one of said

20 angiotensin II receptor antagonist to said aldosterone receptor antagonist.

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15. The method of Claim 14 wherein said weight ratio range is from about five-to-one to about fifteen-to-one.

16. The method of Claim 15 wherein said weight ratio range is about ten-to-one.

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17. The method of Claim 1 wherein said angiotensin II receptor antagonist is selected from the group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,

35 BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22,

WAY-126227, WK-1492.2K, YM-31472, losartan potassium,
E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,
5 L-162441, L-163007, PD-123177, A-81988, BMS-180560,
CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167,
EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739,
HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline,
KRI-1177, L-158809, L-158978, L-159874, LR B087,
10 LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970,
RWJ-46458, S-8307, S-8308, saprisartan, saralasin,
Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731,
BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017,
LY-301875, XH-148, XR-510, zolasartan and PD-123319.

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18. The method of Claim 17 wherein said
angiotensin II receptor antagonist is selected from the
group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170,
20 EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,
BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,
EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,
LY-235656, PD-150304, U-96849, U-97018, UP-275-22,
WAY-126227, WK-1492.2K, YM-31472, losartan potassium,
25 E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,
L-162441, L-163007 and PD-123177.

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19. The method of Claim 1 comprising
administering said combination to treat or prevent the
progression of cardiofibrosis.

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20. The method of Claim 1 comprising
administering said combination to treat or prevent the
progression of cardiac hypertrophy.

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| | | |
|--|-----------|---|
| (51) International Patent Classification ⁶ : A61K 31/585, 45/06, 31/41 // (A61K 45/06, 31:585), (A61K 45/06, 31:41) | A3 | (11) International Publication Number: WO 96/40255 (43) International Publication Date: 19 December 1996 (19.12.96) |
| (21) International Application Number: PCT/US96/08709 (22) International Filing Date: 5 June 1996 (05.06.96) (30) Priority Data: 08/486,085 7 June 1995 (07.06.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/486,085 (CON) Filed on 7 June 1995 (07.06.95) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): EGAN, James, J. [US/US]; 555 Cherry Street, Winnetka, IL 60093 (US). MCMAHON, Ellen, G. [US/US]; 7925 Camelot, St. Louis, MO 63123 (US). OLINS, Gillian, M. [US/US]; 17507 Summit View, Glencoe, MO 63038 (US). SCHUH, Joseph, R. [US/US]; 2055 Rurline Drive, St. Louis, MO 63146 (US). | | (74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 23 January 1997 (23.01.97) |
| (54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST | | |
| (57) Abstract <p>A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9α,11α-substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-{5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl}phenyl]-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.</p> | | |

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/08709

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/585 A61K45/06 A61K31/41 //(A61K45/06,31:585),
(A61K45/06,31:41)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | WO,A,94 09778 (MERCK & CO LTD) 11 May 1994 | 1-20 |
| A | see page 1-2; figures I-XI | |
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| A | see page 21, line 12-20; claims 1-4,6-8 | |
| | see page 24, line 7-12 | 14 |
| | see page 24, line 19-30 | |
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| | --- | |
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

21 November 1996

Date of mailing of the international search report

0 6. 12. 96

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/08709

| C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| A | see page 167 | 13,17,18 |
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| A | see page 226, right-hand column | 13 |
| P,Y | --- WO,A,95 15166 (CURATORS OF THE UNIVERSITY OF MISSOURI) 8 June 1995 | 1-20 |
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| A | --- EP,A,0 122 232 (CIBA-GEIGY AG) 17 October 1984 see page 3, paragraph 5 - page 5, paragraph 4; claims 1-8,10 see page 21, paragraph 2 - page 22, paragraph 1; example 17 ----- | 1-5 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/08709

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-20
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:

Please see next page
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 08709

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the large number of compounds, which are defined by the general formula/description, used in claims 2, 6-12, 17, 18, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, part B, chapter III, paragraph 3.6).

A compound cannot be sufficiently characterized by its pharmacological profile or its mechanism of action as it is done in claim 1 as: "angiotensin II receptor antagonist" and a "aldosterone receptor antagonist". The search has been executed based on compounds specifically mentioned in claims 3-5, 13 and in the examples

Claims searched incompletely: 1, 2, 6-12, 17, 18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/08709

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